(31) Designated countries: AL, AM, AT, AU, AZ, BB, BG, BR, BY,
CA, CH, CN, CZ, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE,
KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,
MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR,
TT, UA, UG, US, UZ, VN, ARIPO Patent (GH, KE, LS, MW, SD,
SZ, UG), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF,
CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published:

With international search report.

(54) **Title:** NEW VITAMIN D DERIVATIVES WITH CARBO- OR
HETEROCYCLIC SUBSTITUENTS AT C-25, PROCESS FOR THEIR
PRODUCTION, INTERMEDIATE PRODUCTS AND USE FOR THE PRODUCTION
OF PHARMACEUTICAL AGENTS

(57) **Abstract**

The invention relates to new vitamin D derivatives of
general formula (I), process for the production, and use for the
production of pharmaceutical agents and intermediate products in
the process.
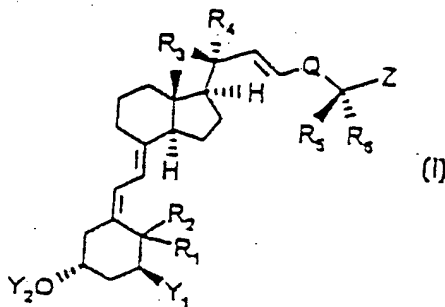
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SN    Senegal
SZ    Swaziland
TD    Chad
TG    Togo
TJ    Tajikistan
TM    Turkmenistan
TR    Turkey
TT    Trinidad and Tobago
UA    The Ukraine
UG    Uganda
US    United States of America
UZ    Uzbekistan
VN    Vietnam
YU    Yugoslavia
ZW    Zimbabwe
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New Vitamin D Derivatives with Carbo- or Heterocyclic
Substituents at C-25, Process for their Production, Intermediate
Products and Use for the Production of Pharmaceutical Agents

This invention relates to vitamin D derivatives with
substituents at C-25 of general formula I

I
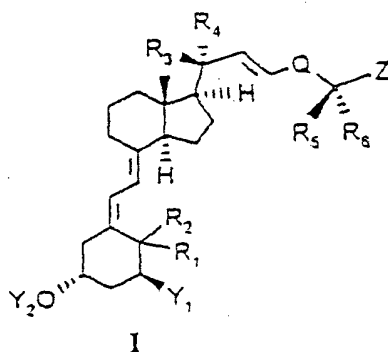
in which

Y$_1$ means a hydrogen atom, a hydroxyl group, an alkanoyloxy
       group with 1 to 12 C atoms or an aroyloxy group,

Y$_2$ means a hydrogen atom or an alkanoyl group with 1 to 12
       C atoms or an aroyl group,

R$_1$ and R$_2$ each mean a hydrogen atom or together an exocyclic
       methylene group,

R$_3$ and R$_4$, independently of one another, mean a hydrogen
       atom, a chlorine or fluorine atom, an alkyl group with
       1 to 4 carbon atoms, together a methylene group or
       together with quaternary carbon atom 20 a 3- to 7-
       membered, saturated or unsaturated carbocyclic ring,

Q   means a straight-chain or branched carbon unit with up
        to 10 carbon atoms, which at any positions can have
        hydroxyl groups (in α- or β-position), which in turn
        can be etherified or esterified, keto groups, amino
        groups or halogen atoms,

R_5 and R_6 at the same time each mean a hydrogen atom, a
        chlorine or fluorine atom, a trifluoromethyl group, a
        straight-chain or branched-chain, saturated or
        unsaturated hydrocarbon radical with up to 4 carbon
        atoms or R_5 and R_6 together with carbon atom 25 mean a
        3- to 7-membered, saturated or unsaturated carbocyclic
        ring and

Z   means a five- or six-membered carbo- or heterocyclic
        ring, which can be saturated, unsaturated or aromatic,
        and at any positions one or more alkyl chains, which
        can be straight-chain or branched, saturated or
        unsaturated, and at any points can be interrupted by
        oxa, thia or aza groups (substituted or unsubstituted)
        or sulfoxide or sulfo groups or can carry substituents
        (hydroxy groups, halogen atoms),

process for their production, intermediate products in the
production process as well as their use for the production of
pharmaceutical agents.

    The alkanoyl or alkanoyloxy groups with 1 to 12 C atoms that
are possible for radicals Y_1 and Y_2 are derived especially from
saturated carboxylic acids. These radicals can be cyclic,
acyclic, carbocyclic or heterocyclic. The preferred radicals are

derived from C_1 to C_9, especially C_2 to C_5 alkanecarboxylic acids, such as, for example, acetyl(oxy), propionyl(oxy), and butyryl(oxy).

As aroyl(oxy) groups, the benzoyl(oxy) groups and substituted benzoyl(oxy) groups are preferred.

For R_3 and R_4, the following preferred combinations apply: R_3 = H, R_4 = methyl or R_3 = methyl, R_4 = H; R_3 = F, R_4 = methyl or R_3 = methyl, R_4 = F; R_3, R_4 = methyl; R_3 and R_4 together form a methylene group or together with tertiary carbon atom 20 form a cyclopropyl ring.

For Q, the following preferences apply:

Q   is an unsubstituted, unbranched alkyl unit with 1, 2 or 3 carbon atoms or

Q   is a hydroxymethylene group (hydroxyl group in α- or ß-position) or

Q = $-CH(OH)-CH_2-$ or $-CH(OH)-CH_2-CH_2-$ (hydroxyl groups in α- or ß-position),

substituents, preferably alkyl groups, for all described variants at C-24a are possible.

For R_5 and R_6, the following preferences apply:

R_5 = R_6 = methyl or ethyl; R_5 and R_6 together with carbon atom C-25 form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring.

Especially preferred are the cases: R_5 = R_6 = methyl, and R_5 and R_6 together with carbon atom C-25 form a cyclopropyl ring.

For Z, the following preferences apply:

For the five-membered case, furan, tetrahydrofuran, thiophene, pyrrole, pyrrolidine, imidazole, pyrazole, oxazole, thiazole, isoxazole, triazole, oxadiazole or thiadiazole rings, which at any positions can carry one or more alkyl chains with 1 to 12 carbon atoms, are preferred. These alkyl chains can be straight-chain or branched, saturated or unsaturated and can be interrupted by heteroatoms (O, S, N also substituted). They can also carry other substituents (hydroxyl groups, halogen atoms).

For the six-membered case, the phenyl, pyridine, pyrazine, pyrimidine, pyridazine, piperidine or tetrahydropyran rings are preferred, which, like the five-membered rings, can be substituted in one or more places with the above-mentioned alkyl chains.

Especially preferred are: imidazole, oxazole, thiazole, furan, thiophene, pyrrole, isoxazole, pyrazole, triazole, pyridine, pyrimidine and phenyl rings, which each carry a straight-chain, saturated C1 to C12 alkyl chain.

Especially preferred according to this invention are the following compounds:

(5Z,7E,22E)-(1S,3R,24R)-25-(5-Propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-ethylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-pentylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-pentylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-propylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-propylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-methylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-methylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-ethylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-butylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-butylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-pentylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-pentylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-propylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-propylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-methylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-methylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-ethylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-butylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-butylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-pentylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-pentylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-propylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-propylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-methylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-methylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-ethylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-butylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-butylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-pentylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-pentylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-propylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-propylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-methylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-methylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-ethylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-butylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-butylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-pentylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-pentylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-ethylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-pentylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-pentylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-propylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-propylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-methylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-methylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-ethylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-butylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-butylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-pentylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-pentylimidazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-propylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-propylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-methylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-methylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-ethylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-butylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-butylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-pentylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-pentylfuran-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-propylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-propylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-methylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-methylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-ethylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-butylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-butylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-pentylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-pentylthiophen-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-propylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-propylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-methylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-methylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-ethylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-butylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-butylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-pentylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-pentylpyrrol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(3-methyl-1,2,4-oxadiazol-5-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(3-methyl-1,2,4-oxadiazol-5-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(3-ethyl-1,2,4-oxadiazol-5-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(3-ethyl-1,2,4-oxadiazol-5-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(3-propyl-1,2,4-oxadiazol-5-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(3-propyl-1,2,4-oxadiazol-5-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(3-butyl-1,2,4-oxadiazol-5-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(3-butyl-1,2,4-oxadiazol-5-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(3-pentyl-1,2,4-oxadiazol-5-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(3-pentyl-1,2,4-oxadiazol-5-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-methyl-1,3,4-oxadiazol-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-methyl-1,3,4-oxadiazol-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethyl-1,3,4-oxadiazol-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-ethyl-1,3,4-oxadiazol-2-yl)-

26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-propyl-1,3,4-oxadiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-propyl-1,3,4-oxadiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-butyl-1,3,4-oxadiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-butyl-1,3,4-oxadiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-pentyl-1,3,4-oxadiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-pentyl-1,3,4-oxadiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-phenyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-phenyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-methylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-methylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-ethylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-propylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-propylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-pentylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-pentylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(3-methylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(3-methylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(3-ethylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(3-ethylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(3-propylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(3-propylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(3-butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(3-butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(3-pentylphenyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(3-pentylphenyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-[4-(1-methylethyl)phenyl]-26,27-
cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-[4-(1-methylethyl)phenyl]-26,27-
cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-[3-(1-methylethyl)phenyl]-26,27-
cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-[3-(1-methylethyl)phenyl]-26,27-
cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(2-pyridyl)-26,27-cyclo-9,10-
secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(2-pyridyl)-26,27-cyclo-9,10-
secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(6-methyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(6-methyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-methyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-methyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-methyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-methyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(6-ethyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(6-ethyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-ethyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-ethyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(6-propyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(6-propyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-propyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-propyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-propyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-propyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(6-butyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(6-butyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-butyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-butyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-butyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-butyl-2-pyridyl)-26,27-cyclo-
9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5,5-dimethyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5,5-dimethyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5,5-diethyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5,5-diethyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24R,25(R)]-25-(5-methyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24S,25(R)]-25-(5-methyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24R,25(S)]-25-(5-methyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24S,25(S)]-25-(5-methyl-2-oxazolin-2-yl)-

26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24R,25(R)]-25-(5-ethyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24S,25(R)]-25-(5-ethyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24R,25(S)]-25-(5-ethyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24S,25(S)]-25-(5-ethyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24R,25(R)]-25-(5-propyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24S,25(R)]-25-(5-propyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24R,25(S)]-25-(5-propyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24S,25(S)]-25-(5-propyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24R,25(R)]-25-(5-butyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24S,25(R)]-25-(5-butyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24R,25(S)]-25-(5-butyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24S,25(S)]-25-(5-butyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24R,25(R)]-25-(5-phenyl-2-oxazolin-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24S,25(R)]-25-(5-phenyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24R,25(S)]-25-(5-phenyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-[1S,3R,24S,25(S)]-25-(5-phenyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-ethylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-ethylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-pentylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-pentylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(4-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(4-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(4-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(4-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(4-ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(4-ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(4-butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(4-butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(4-pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(4-pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(4-propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(4-propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(4-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(4-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(4-ethylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(4-ethylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(4-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(4-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24R)-25-(4-pentylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(4-pentylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(5-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-20-methyl-25-(5-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(5-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-20-methyl-25-(5-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethyloxazol-2-yl)-20-methyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-ethyloxazol-2-yl)-20-methyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-butyloxazol-2-yl)-20-methyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-butyloxazol-2-yl)-20-methyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(5-pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-20-methyl-25-(5-pentyloxazol-2-yl)-

26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(5-propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-20-methyl-25-(5-propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(5-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-20-methyl-25-(5-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethylthiazol-2-yl)-20-methyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-ethylthiazol-2-yl)-20-methyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-butylthiazol-2-yl)-20-methyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-butylthiazol-2-yl)-20-methyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(5-pentylthiazol-2-yl)-20-methyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(5-pentylthiazol-2-yl)-20-methyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(4-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-20-methyl-25-(4-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(4-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-20-methyl-25-(4-methyloxazol-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethyloxazol-2-yl)-20-methyl-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-ethyloxazol-2-yl)-20-methyl-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-butyloxazol-2-yl)-20-methyl-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-butyloxazol-2-yl)-20-methyl-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(4-pentyloxazol-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-20-methyl-25-(4-pentyloxazol-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(4-propylthiazol-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-20-methyl-25-(4-propylthiazol-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(4-methylthiazol-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-20-methyl-25-(4-methylthiazol-2-yl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethylthiazol-2-yl)-20-methyl-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-ethylthiazol-2-yl)-20-methyl-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-butylthiazol-2-yl)-20-methyl-

26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-butylthiazol-2-yl)-20-methyl-

26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24R)-25-(4-pentylthiazol-2-yl)-20-methyl-

26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

(5Z,7E,22E)-(1S,3R,24S)-25-(4-pentylthiazol-2-yl)-20-methyl-

26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol

The natural vitamins D_2 and D_3 (cf. general formula of
vitamin D) are inherently biologically inactive and are converted
into biologically active metabolites [1α,25-dihydroxy vitamin D_3
(calcitriol) or -D_2] only after hydroxylation at C-atom 25 in the
liver and at C-atom 1 in the kidney. The action of the active
metabolites involves the regulation of the calcium and phosphate
concentration in the serum; they counteract a dropping of the
calcium concentration in the serum by increasing the calcium
absorption in the intestine and under certain circumstances
promoting calcium mobilization from the bones.
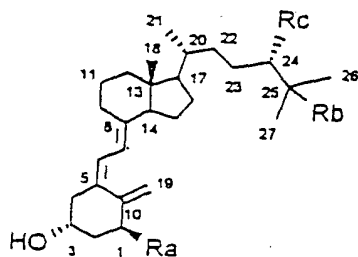
Ergocalciferol: Ra=Rb=H, Rc=CH_3 vitamin D_2
Double bond C-22/23

Cholecalciferol: Ra=Rb=Rc=H   vitamin D_3
25-hydroxycholecalciferol: Ra=Rc=H, Rb=OH
1α-hydroxycholecalciferol: Ra=OH, Rb=Rc=H
1α,25-dihydroxycholecalciferol: Ra=Rb=OH,
                                Rc=H   Calcitriol

In addition to their pronounced effect on the calcium and
phosphate metabolism, the active metabolites of vitamins D_2 and

D_3 and their synthetic derivatives have a proliferation-inhibiting and differentiation-stimulating action on tumor cells and normal cells, such as, for example, skin cells. In addition, a pronounced effect on cells of the immune system (inhibiting of proliferation and interleukin 2-synthesis of lymphocytes, increase of cytotoxicity and phagocytosis in vitro of monocytes) has been found, which manifests itself in an immunomodulatory action, and finally, because of a stimulating action on bone-forming cells, an increased formation of bone in normal and osteoporotic rats is found [R. Bouillon et al. "Short Term Course of $1,25(OH)_2D_3$ Stimulates Osteoblasts But Not Osteoclasts." Calc. Tissue Int. **49**, 168-173 (1991)].

All actions are mediated by bonding to the vitamin D receptor. Because of the bonding, the activity of specific genes is regulated.

When using biologically active metabolites of vitamins D_2 and D_3, a toxic effect on the calcium metabolism is produced (hypercalcemia).

By structural manipulations of the side chain, therapeutically usable effectiveness can be separated from undesirable hypercalcemic activity. A suitable structural variant is the introduction of 24-hydroxy derivatives.

1α-Cholecalciferols that are hydroxylated in 24-position are already described in DE 25 26 981. They have a lower toxicity than the corresponding non-hydroxylated 1α-cholecalciferol. Further, 24-hydroxy derivatives are described in the following

patent applications: DE 39 33 034, DE 40 03 854, DE 40 34 730, EP 0 421 561, EP 0 441 467, WO 91/12238.

Finally, 25-carboxylic acid derivatives of calcitriol that are hydroxylated at C-24 are described in WO 94/07853, which exhibit a more advantageous spectrum of action than calcitriol. While the ability to trigger a hypercalcemia is considerably weakened, the proliferation-inhibiting and differentiation-stimulating actions are maintained.

Relative to these structurally allied compounds, the substances according to the invention are distinguished in that they show a greater effect on cell differentiation, whereby the effect on the calcium balance does not increase. Other substances according to the invention, however, exhibit an antagonistic profile of action that can make new applications possible.

The vitamin D activity of the substances according to the invention is determined with the aid of the calcitriol-receptor test. It is carried out using a specific receptor protein from the intestines of juvenile pigs.

Receptor-containing binding protein is incubated in a test tube with ^{3}H-calcitriol (5×10^{-10} mol/l) in a reaction volume of 0.270 ml in the absence and in the presence of test substances for two hours at 4°C. To separate free and receptor-bound calcitriol, a charcoal-dextran absorption is carried out. 250 μl of a charcoal-dextran suspension is fed to each test tube and incubated at 4°C for 20 minutes. Then, the samples are centrifuged at 10,000 x g for 5 minutes at 4°C. The supernatant

is decanted and measured in a ß-counter after 1 hour of equilibration in Picofluor 15[TM].

The competition curves that are obtained with various concentrations of test substance as well as of reference substance (unlabeled calcitriol) at constant concentration of the reference substance (^{3}H-calcitriol) are placed in relation to one another, and a competition factor (KF) is determined.

It is defined as a quotient of the concentrations of the respective test substance and the reference substance, which are necessary for 50% competition:

KF = Concentration of test substance at 50% competition

Concentration of reference substance at 50% competition

It is common to the compounds according to the invention that they all have a considerable affinity to the calcitriol receptor.

To determine the acute hypercalcemic action of various calcitriol derivatives, the test that is described below is carried out:

The action of control (solution base), reference substance (1,25(OH)$_2$-D$_3$=calcitriol) and test substance is tested in each case after one-time subcutaneous administration in groups of 10 healthy male rats (140-170 g). During the testing time, the rats are kept in special cages to determine the excretion of water and mineral substances. Urine is collected in 2 fractions (0-16 hours and 16-22 hours). An oral dose of calcium (0.1 mmol of calcium in 6.5% alpha-hydroxypropylcellulose, 5 ml/animal) replaces at 1600 hours the calcium intake that is lacking by food

deprivation. At the end of the test, the animals are killed by decapitation and exsanguinated to determine the serum-calcium values. For the primary screen test in vivo, an individual standard dose (200 μg/kg) is tested. For selected substances, the result is supported by establishing a dose-effect relation.

A hypercalcemic action is shown in serum-calcium level values that are higher than in the control.

The significance of differences between substance groups and controls and between test substance and reference substance are supported with suitable statistical processes. The result is indicated as dose ratio DR (DR = factor of test substance dose/reference substance dose for comparable actions).

The differentiation-stimulating action of calcitriol analogues is also detected quantitatively.

It is known in the literature [Mangelsdorf, D. J. et al., J. Cell. Biol. 98: 391 (1984)], that the treatment of human leukemia cells (promyelocyte cell line HL 60) in vitro with calcitriol induces the differentiation of cells to macrophages.

HL 60 cells are cultivated in tissue culture medium (RPMI 10% fetal calf serum) at 37°C in an atmosphere of 5% CO_2 in air.

For substance testing, the cells are centrifuged off, and 2.0 x 10^5 cells/ml in phenol red-free tissue culture medium is taken up. The test substances are dissolved in ethanol and diluted with tissue culture medium without phenol red to the desired concentration. The dilution stages are mixed with the cell suspension at a ratio of 1:10, and 100 μl each of this cell suspension that is mixed with substance is pipetted into an

indentation of a 96-hole plate. For control, a cell suspension is mixed analogously with the solvent.

After incubation for 96 hours at 37°C in 5% CO_2 in air, 100 μl of an NBT-TPA solution (nitro blue tetrazolium (NBT), final concentration in the batch of 1 mg/ml, tetradecanoyl phorbolmyristate-13-acetate (TPA), final concentration in the batch of 2 x 10^{-7} mol/l) is pipetted into each indentation of the 96-hole plate in the cell suspension.

By incubation for 2 hours at 37°C and 5% CO_2 in air, NBT is reduced to insoluble formazan because of the intracellular oxygen radical release, stimulated by TPA, in the cells that are differentiated to macrophages.

To complete the reaction, the indentations of the 96-hole plate are suctioned off, and the cells are affixed to the bottom of the plate by adding methanol and dried after affixing. To dissolve the intracellular formazan crystals that are formed, 100 μl of potassium hydroxide (2 mol/l) and 100 μl of dimethyl sulfoxide are pipetted into each indentation and ultrasonically treated for 1 minute. The concentration of formazan is measured by spectrophotometry at 650 nm.

As a yardstick for the differentiation induction of HL 60 cells to macrophages, the concentration of formed formazan applies. The result is indicated as a dose ratio (DR = factor of test substance dose/reference substance dose for comparable semi-maximum actions).

The results of the calcitriol-receptor test and the determination of the dose ratio of the differentiation induction

of HL 60 cells and the dose ratio for hypercalcemia are summarized below:

Test compounds:

(5Z,7E,22E)-(1S,3R,24R)-25-(5-Propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **14**

(5Z,7E,22E)-(1S,3R,24R)-25-(5-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **15**

(5Z,7E,22E)-(1S,3R,24R)-25-(5-ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **16**

(5Z,7E,22E)-(1S,3R,24R)-25-(5-pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **17**

Comparison compound:
Calcitriol

Compound	Competition Factor KF for Receptor Bonding	Dose Ratio for Differentiation Induction in HL 60 Cells
14	2	1.9
15	2	3.4
16	3	1.3
17	4	>100
calcitriol	1	1

In addition to an affinity to the vitamin D receptor, which is comparable to that of calcitriol, the compounds listed partially show a likewise comparable cell-differentiating activity.

The induction of a hypercalcemia is carried out, however, only at very much higher doses than in the case of calcitriol (dose ratio for **14** = 300; calcitriol DR = 1).

By the reduced property of triggering a hypercalcemia, the substances according to the invention are suitable in a special way for the production of pharmaceutical agents for the treatment of diseases that are characterized by hyperproliferation and deficient cell differentiation. Included in these are, for example, hyperproliferative diseases of the skin (psoriasis, pityriasis subia pilasis, acne, ichthyosis) as well as tumor diseases and precancerous stages (for example, tumors of the intestines, carcinomas of the breast, lung tumors, prostate carcinomas, leukemias, T-cell lymphomas, melanomas, Batazell Larzin, squamous carcinoma, actinic keratoses, cervix dysplasias, and metastasizing tumors of any type).

Also, for the treatment and prophylaxis of diseases that are characterized by a disequilibrium of the immune system, the substances according to the invention are suitable. These include eczemas and diseases of the atopic Formon series, as well as auto-immune diseases, such as, for example, multiple scleroses, diabetes mellitus type I, myasthenia gravis, lupus erythematosus, scleroderma, bullous skin diseases (pemphigus, pemphigoid), further rejection reactions in the case of

autologous, allogeneic or xenogeneic transplants, as well as AIDS. In all these diseases, the new compounds of general formula I can be combined advantageously with other substances that have an immunosuppressive action, such as cyclosporin A, FK 506, rapamycin and anti-CD 4 antibodies.

The substances are also suitable for therapy of secondary hyperparathyroidism and renal osteodystrophia because of the property of calcitriols to drop the parathormone synthesis.

Owing to the presence of the vitamin D receptor in the insulin-producing cells of the pancreas, the substances are suitable by increasing the insulin secretion for the therapy of diabetes mellitus type II.

Further, it has been found, surprisingly enough, that by topical application of the compounds according to the invention on the skin of mice, rats and guinea pigs, an increased reddening of the skin and increase of the thickness of the epidermis can be induced. The increase in the reddening of the skin is determined from the increase in the red value of the skin surface that can be quantified with a colorimeter. The red value is typically increased 1.5-fold after the substance (dose 0.003%) is administered three times at intervals of 24 hours. The increase of the thickness of the epidermis is quantified in the histological preparation. It is typically increased 2.5-fold. The number of proliferating epidermal cells (cells in the S-phase of the cell cycle) is determined by flow cytometry and is typically increased by a factor of 6.

These properties of the derivatives in the vitamin D series according to the invention can appear suitable for therapeutic use in the case of atrophic skin, as it occurs in natural skin aging because of increased light exposure or medicinally-induced skin atrophy by treatment with glucocorticoids.

Further, it can be assumed that wound healing can be accelerated by topical application with the new compounds.

In cell populations of the hair follicle, which contribute decisively to hair growth or to hair cycle regulation, it was possible to detect vitamin D_3 receptor proteins [Stumpf, W. E. et al., **Cell Tissue Res.** **238**: 489 (1984); Milde, P. et al., J. **Invest. Dermatol.**, **97**: 230 (1991)]. In addition, in vitro findings on isolated hair follicle keratinocytes show a proliferation-inhibiting and differentiation-stimulating influence of $1,25-(OH)_2-D_3$.

From clinical observations, it is known that the vitamin D_3-resistant rickets often accompanies alopecia, which develops in early infancy. Experimental findings show that the vitamin D_3 binding site of the VDR in this disease mutates, i.e., is defective (Kristjansson, K. et al., **J. Clin. Invest.** **92**: 12, 1993)]. Keratinocytes, which were isolated from the hair follicles of these patients, do not react in vitro to the addition of $1,25-(OH)_2-D_3$ [Arase, S. et al., **J. Dermatol. Science** **2**: 353 (1991)].

These findings indicate a decisive role for $1,25-(OH)_2-D3$ in the regulation of hair growth.

These analogues are therefore especially suitable for the production of pharmaceutical agents for the treatment of diseases which accompany disrupted hair growth (androgenetic alopecia, alopecia areata/totalis, chemotherapy-induced alopecia) or for supporting physiological hair growth.

Senile and postmenopausal osteoporosis is characterized by an increased bone turnover with an overall negative balance. Owing to the bone shrinkage especially of trabecular bones, fractures result to an increased extent. Owing to the stimulating action of calcitriol, both in the number and the conduct of synthesis of cells forming new bones (osteoblasts), the substances according to the invention are suitable for therapy and prophylaxis of senile and postmenopausal osteoporosis (EP 0 634 173 A1), of steroid-induced osteoporosis as well as for accelerated healing of arthroplasties. For the therapy of various forms of osteoporosis, they can be combined advantageously with estradiol or other derivatives of estrogen.

Finally, it was possible to show that calcitriol increases the synthesis of a growth substance for nerve cells (nerve growth factor) [M. S. Saporito et al. **Brain Res.** 633, 189 (1994)]. The compounds according to the invention are therefore also suitable for treating degenerative diseases of the peripheral and central nervous system, such as Alzheimer's disease and amyotrophic lateral sclerosis.

In addition, it has been found that certain compounds of general formula I in HL 60 cells antagonize, surprisingly enough, the action of calcitriol. In the series of 25-oxazole

derivatives, the compounds with increasing chain length on the heterocycle in the case of constantly good receptor affinity show considerably weaker differentiation-stimulating agonistic activity in HL 60 cells (Tab. 1). Compounds **16** and **17** antagonize the action of calcitriol in HL 60 cells. This property is continued with increasing chain length in radical Z of general formula I.

Such compounds that antagonize the action of calcitriol can be used for the therapy of hypercalcemias, such as, for example, in hypervitaminosis D or intoxication with calcitriol and calcitriol-like active substances, or in the case of increased extrarenal calcitriol synthesis in granulomatous diseases (sarcoidosis, tuberculosis). Also, paraneoplastic hypercalcemias (for example, in osteolytic metastases and tumors with increased synthesis of parathormone-related peptides) as well as in hypercalcemias in hyperparathyroidism.

In addition, calcitriol antagonists can be used for birth control. In the reproductive tracts of female and male animals, the vitamin D receptor is expressed. It is known that the female and male fertility of vitamin-D-deficient animals is reduced. By short-term substitution of calcitriol, the reproductive output can be increased. Calcitriol antagonists are therefore able to influence female and male fertility.

Since calcitriol, under certain conditions, shows an immunosuppressive action, calcitriol receptor antagonists can also be used as immunostimulants, e.g., in the case of weak defenses against infections.

Calcitriol is known to be able to modulate hair growth. Calcitriol antagonists can therefore be used therapeutically in the case of undesirable hair growth, e.g., in hirsutism.

Vitamin D has long been known to play a stimulating role in the formation of arteriosclerotic plaque. In such vascular lesions, a calcitriol-regulated protein, osteopontin, is found to be increased, to which a role in vascular sclerosis is attributed [R. Eisenstein et al. **Arch. Path.** 77, 27 (1964), L. A. Fitzpatrick et al., **J. Clin. Invest.** 94, 1597 (1994)]. Calcitriol antagonists are therefore suitable for therapy and prophylaxis of all types of arteriosclerosis.

Finally, calcitriol antagonists are suitable because of the property of calcitriol to increase unspecific immune reactions of monocytic cells, for therapy of inflammatory diseases, especially of a chronic nature, such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, and granulomatous diseases such as sarcoidosis and other foreign-body reactions.

This invention thus relates to pharmaceutical preparations that contain at least one compound according to general formula I together with a pharmaceutically compatible vehicle.

The compounds can be formulated as solutions in pharmaceutically compatible solvents or as emulsions, suspensions or dispersions in suitable pharmaceutical solvents or vehicles or as pills, tablets or capsules, which contain solid vehicles in a way known in the art. For topical use, the compounds are advantageously formulated as creams or ointments or in a similar form of pharmaceutical agent that is suitable for topical use.

Each such formulation can also contain other pharmaceutically compatible and nontoxic adjuvants, such as, e.g., stabilizers, antioxidants, binders, dyes, emulsifiers or flavoring additives. The compounds are advantageously administered by injection or intravenous infusion of suitable sterile solutions or as oral dosage via the alimentary tract or topically in the form of creams, ointments, lotions or suitable transdermal patches, as is described in EP-A 0 387 077.

The daily dose is approximately 0.1 μg/patient/day - 1000 μg (1 mg)/patient/day, preferably 1.0 μg/patient/day - 500 μg/patient/day.

Vitamin D derivatives with substituents at C-25 are already described in Patent Application WO 97/00242 (Schering AG). In all cases, however, the substituent is linked by a carbonyl group, a hydroxymethyl group or a double bond to carbon atom 25. Under no circumstances did linkage of carbon atom directly to a carbo- or heterocycle occur. The synthesis methods described do not allow the creation of such substitution models, so that new processes had to be developed.

The production of the vitamin D derivatives of general formula I is carried out according to the invention from a compound of general formula II,

II
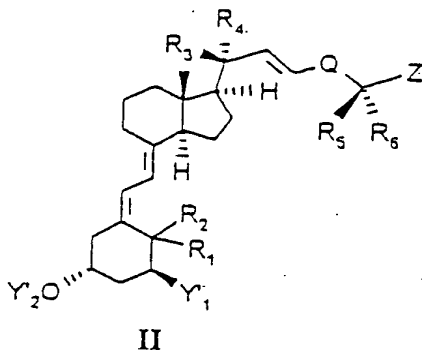
in which Y'$_1$ means a hydrogen atom or a protected hydroxyl group and Y'$_2$ means a hydroxy protective group.

Z' is distinguished from Z in that optionally present hydroxyl groups can be present in protected form.

The protective groups are preferably alkyl-, aryl- or mixed alkylaryl-substituted silyl groups, e.g., the trimethylsilyl (TMS), triethylsilyl (TES), **tert**-butyldimethylsilyl (TBDMS), **tert**-butyldiphenylsilyl (TBDPS) or triisopropylsilyl (TIPS) groups or another standard hydroxy protective group (methoxymethyl, methoxyethoxymethyl, ethoxyethyl, tetrahydrofuranyl-tetrahydropryanl groups or see T. W. Greene, P. G. M. Wuts "Protective Groups in Organic Synthesis," 2nd Edition, John Wiley & Sons, 1991).

By simultaneous or successive cleavage of the hydroxy protective groups and optionally by partial, successive or complete esterification of the free hydroxyl groups, II is converted into a compound of general formula I.

In the case of the silyl protective groups or the trimethylsilylethoxymethyl group, tetrabutylammonium fluoride, hydrofluoric acid or hydrofluoric acid/pyridine is used for their cleavage; in the case of the ether groups (methoxymethyl, methoxyethoxymethyl, ethoxyethyl, tetrahydropyranylether), the latter are cleaved under catalytic action of acid, for example, p-toluenesulfonic acid, pyridinium-p-toluenesulfonate, acetic acid, hydrochloric acid, phosphoric acid or an acidic ion exchanger.

The esterification of the free hydroxy groups can be carried out according to standard processes with the corresponding carboxylic acid chlorides, bromides or anhydrides.

The production of the starting compounds for general formula II starts from various starting compounds depending on the ultimately desired substitution pattern in 10- and 20-position.

For the production of compounds of general formula II, in which R_1 and R_2 together mean an exocyclic methylene group, a start is made from known aldehyde III [M. Calverley Tetrahedron **43**, 4609 (1987), WO 87/00834].

III
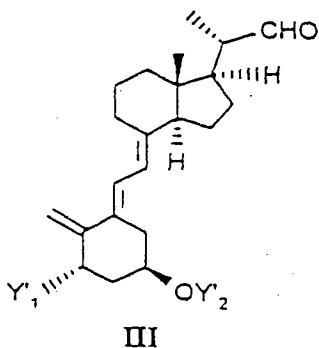
For Y'_1 and Y'_2, the already mentioned definitions apply. Protective groups other than those mentioned in the bibliographic references can be obtained by analogous procedure using correspondingly modified silyl chlorides (e.g., **tert-butyldiphenylsilyl** chloride instead of **tert-butyldimethylsilyl** chloride). By foregoing the corresponding stages for 1α-hydroxylation, derivatives of Y'_1 = H type can be obtained.

The compounds of general formula III are now converted, analogously to known processes, into aldehydes of general formula

IV [EP 647 219, WO 94/07853, M. J. Calverley, L. Binderup Bioorg. Med. Chem. Lett. $\underline{3}$, 1845-1848 (1993)].

IV
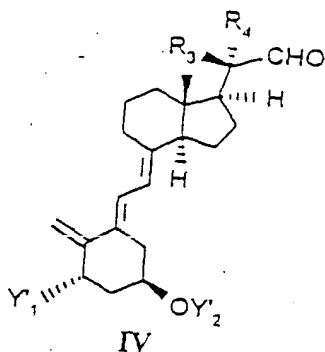
For R_3 and R_4, the definitions that are already mentioned above apply.

In creating the side chain, both compounds of general formula III and compounds of general formula IV can now be used.

Analogously to the established sequence (WO 94/07853), carboxylic acid amides of general formula V can thus be generated,

V
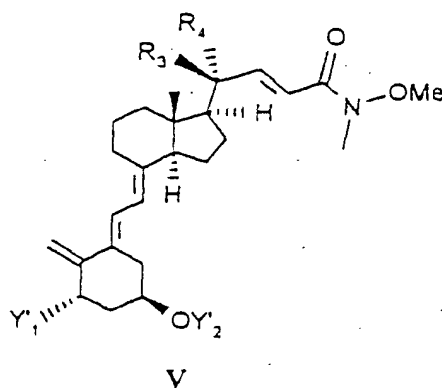
whereby for Y'_1, Y'_2, R_3 and R_4, the already given definitions apply.

To establish the natural vitamin D-triene system, a photochemical isomerization of the compounds of general formula V

44

is performed.   Irradiation with ultraviolet light is carried out

in the presence of a so-called triplet sensitizer.   Within the

scope of this invention, anthracene is used in this respect.   By

cleavage of the π-bond of the 5,6-double bond, rotation of the A

ring by 180° around the 5,6-single bond and reestablishing the

5,6-double bond, the stereoisomerism on the 5,6-double bond is

reversed, whereby compounds of general formula **VI** accumulate,

VI
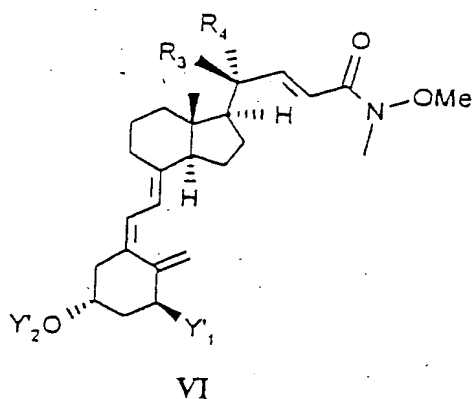
whereby Y'_1, Y'_2, R_3 and R_4 have the above-mentioned meanings.

With a reducing agent (e.g., lithium aluminum hydride or

diisobutylaluminum hydride), the amide group in the compound of

general formula **VI** is reduced to aldehyde at low temperature

(-60°C to -100°C) in a solvent such as tetrahydrofuran or another

ether, whereby a compound of general formula **VII** accumulates,

VII
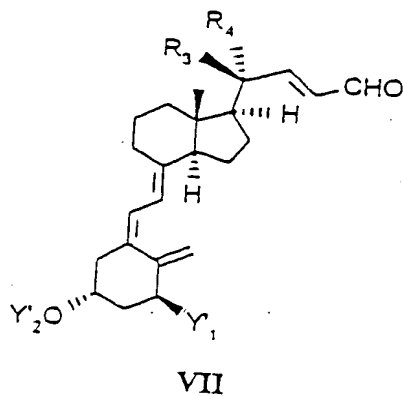
whereby radicals Y'_1, Y'_2, R_3 and R_4 have the already mentioned meanings.

The side chain now builds up further at the compound of general formula **VII**. By way of example, a description is given below of the use of the aldehyde of general formula **VII** for which the following is true: R_3 = H and R_4 = methyl. Correspondingly, however, the reaction possibilities below also apply for all other definitions for R_3 and R_4.

For synthesis of calcitriol derivatives with 26,27-cyclomodification, which, moreover, have oxazole substituents at C-25, the following synthesis method can be employed. Starting from 1-bromocyclopropanecarboxylic acid **VIII** [H. M. R. Hoffmann et al. **J. Org. Chem.** <u>54</u>, 6096 (1989)], suitable side-chain fragments can be prepared.

$$\text{Br} \quad \text{COOH}$$
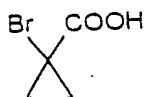
VIII

The reaction with amino ketones or their hydrochlorides [M. Jackson et al., **J. Am. Chem. Soc.** <u>70</u>, 2884 (1948), J. D. Hepworth **Org. Synth.** <u>45</u>, 1 (1965)] of general formula **IX** first is carried out under condensation conditions (e.g., N,N'-dicyclohexyl-carbodiimide, triethylamine),

$$\text{(HCl)} \quad \overset{O}{\underset{R'_7}{H_2N\diagdown\diagup R_7}}$$
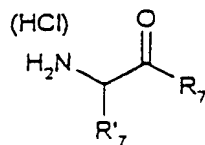
IX

whereby R_7 and R'_7, independently of one another, mean a hydrogen atom, a straight-chain or branched, saturated or unsaturated alkyl radical with up to 12 carbon atoms, which can be interrupted at any points by oxa, thia or aza groups (substituted or unsubstituted) or sulfoxide or sulfo groups or can carry other substituents (free or protected hydroxy groups, halogen atoms). Derivatives of general formula X are thus produced.
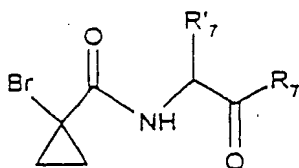
X

As an alternative, aminoalcohols or protected aminocarbonyl compounds can also be reacted with carboxylic acid VIII. The formation of derivatives of general formula X is then carried out by oxidation or protective group cleavage.

The formation of the oxazole ring can now be carried out under the effect of acid (e.g., sulfuric acid, phosphoric acid, polyphosphoric acid), whereby derivatives of general formula XI accumulate. Especially for the case R_7 = H, gentler methods for oxazole formation are to be preferred [e.g., PPh_3, NEt_3, I_2 or C_2Cl_6, C. J. Moody et al. **Synlett** 825 (1996), W. Steglich et al. **Lieb. Ann.** 1916 (1978)].
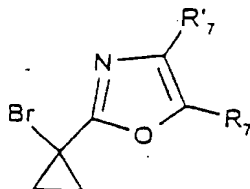
XI

The creation of the side chain is now carried out by reaction of the cyclopropyl-metal compound that is generated by bromine-metal exchange from **XI** and vitamin D-C-24-aldehyde **VII**. The use of **n**-butyllithium or **tert**-butyllithium in hexane, diethyl ether, tetrahydrofuran or mixtures of these solvents is advantageous here at temperatures of between -100°C and -50°C. Derivatives of general formula **XII** are thus obtained.

XII
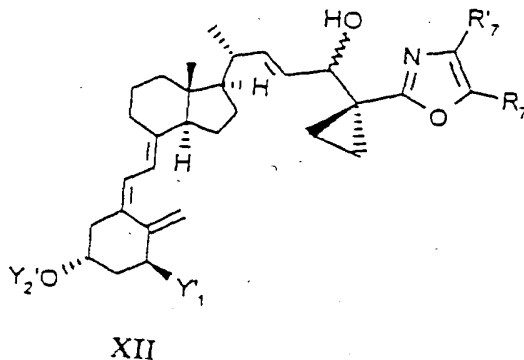
The latter can be regarded as a special case of general formula **II**, whose further reaction was already described and for which the following applies: Q is a hydroxymethylene group, R_1 and R_2 together form a methylene group, R_5 and R_6 together with carbon atom C-25 form a cyclopropyl ring, and Z′ is an oxazole with substituents R_7 or R'_7, which has been defined previously.

The diastereomers can be separated relative to carbon atom C-24 chromatographically at this or a later stage.

A similar synthesis method can result in calcitriol derivatives that carry thiazole substituents at C-25. The derivative of general formula **X** must then be reacted in the

presence of a sulfur reagent, such as, e.g., phosphorus pentasulfide, whereby thiazole derivatives of general formula XIII accumulate.
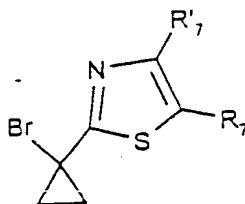
XIII

As an alternative, derivatives of general formula XIII for which R_7 = hydrogen and R'_7 has the previously mentioned meaning could be obtained by reaction of corresponding amide VIII′ to carboxylic acid VIII [H. M. R. Hoffmann et al. J. Org. Chem. 54, 6096 (1989)]

VIII′

with 1-bromoketone ($BrCH_2$-CO-R'_7) in the presence of a sulfur reagent such as phosphorus pentasulfide [R. Kurkjy et al. J. Am. Chem. Soc. 74, 5778 (1952), G. Schwarz Org. Synth. Coll. Vol. III, 332].

For synthesis of the derivatives of general formula XIII for which R_7 can have the previously mentioned meaning, and R'_7 = hydrogen, however, amide VIII′ must be reacted with 2-bromaldehydes (OHC-CHBr-R_7) in the presence of phosphorus pentasulfide.

For synthesis of calcitriol derivatives, which carry imidazole substituents at C-25, the derivative of general formula X can be reacted in the presence of primary amines such as R_8NH_2, whereby imidazole derivatives of general formula XIV are produced.

XIV
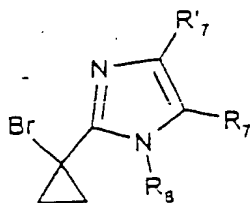
Substituent R_8 can be a hydrogen atom or a straight-chain or branched, saturated or unsaturated alkyl radical with up to 12 carbon atoms.

In addition, the creation of imidazole systems can also be carried out from amidine VIII" that corresponds to carboxylic acid VIII
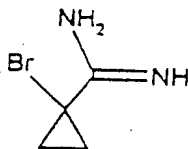
VIII"

with 1-bromoketones ($Br-CH_2-CO-R_7$) or 2-bromaldehydes ($OHC-CHBr-R'_7$).

The linkage of thiazole or imidazole fragments can be carried out as described for the oxazole case, whereby derivatives of general formula XV are produced. In the case of several acid hydrogen atoms, either a suitable protective group

technique must be used or the selective halogen/lithium exchange has to be carried out on bromocyclopropane by setting very low temperatures (-130 to -100°C).
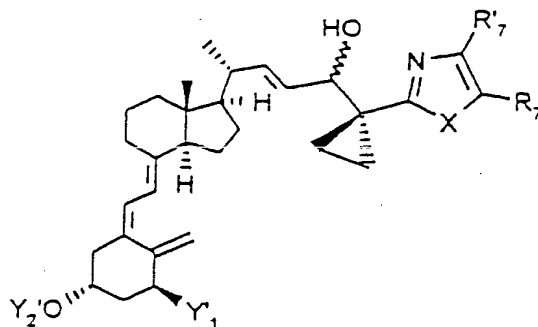
XV

In general formula **XV**, X can mean a sulfur atom or the previously defined unit $N-R_8$. All other radicals and the further treatment of the derivatives of general formula **XV** have been described previously.

Starting from carboxylic acid **VIII** or derivatives thereof (esters, amides, acid chlorides), 1,4-diketones of general formula **XVI** can be generated under standard reaction conditions [for use of functionalized organometallic reagents, see, e.g., M. Yus et al. **J. Org. Chem.** <u>56</u>, 3825 (1991), J. Barluenga et al. **J. Chem. Soc. Perk.** I 3113 (1988), followed by manipulations of the functional groups such as, e.g., ketal cleavages].
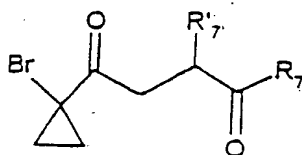
XVI

By using the reaction conditions that were already used for the reaction of the derivatives of general formula **X** (action of acid, phosphorus pentasulfide or the like, or primary amines such as R_8NH_2), furan, thiophene or pyrrole derivatives of general formula **XVII** can be obtained,
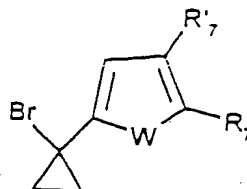
XVII

whereby W can mean an oxygen atom, a sulfur atom or the $N-R_8$ group.

The linkage to the vitamin D system is carried out analogously to the previously described cases, whereby derivatives of general formula **XVIII** accumulate.
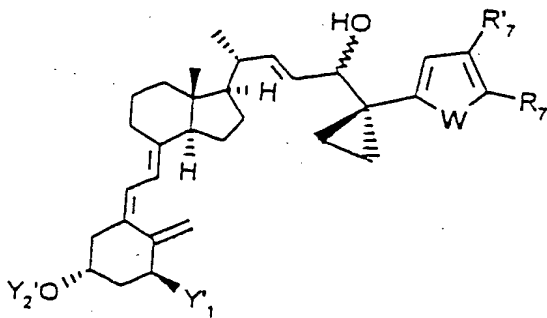
XVIII

The subsequent reaction steps as well as the radicals have already been described previously.

Carboxylic acid **VIII** can also be converted into other suitable components. Thus, aldehyde **IXX** can be produced by reduction of the carboxylic acid or a derivative (acid chloride, ester, amide -- especially N-methoxy-N-methylamide) and optionally reoxidation.
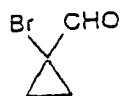
IXX

Acetylene derivative **XX** is obtained by reaction with the Seyferth reagent [S. Schreiber et al. **J. Am. Chem. Soc.** 112, 5583 (1990)] or under Corey-Fuchs conditions [P. Ma et al. **Synth. Comm.** 25, 3641 (1995)].
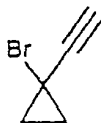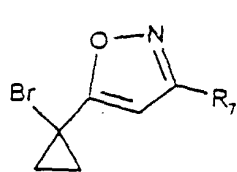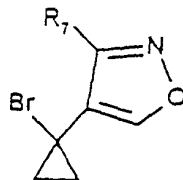

XX

Heterocycles of general formulas **XXIa** and **XXIb** (isoxazoles), **XXIIa** and **XXIIb** (pyrrazole) as well as **XXIIIa** and **XXIIIb** (triazole) can be produced by 1,3-dipolar cycloadditions with nitrile oxides ($R_7-C \equiv N-O^-$), diazo compounds ($R_7-CH^--N \equiv N^+$) or
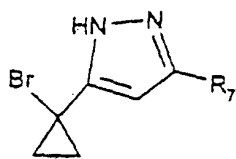
alkylazides $(R_7-N^--N=N^+)$.

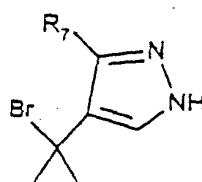
XXIa   XXIb

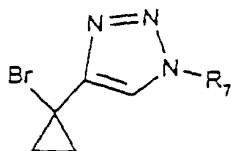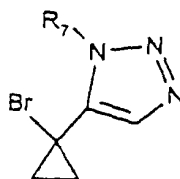XXIIa   XXIIb
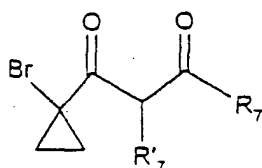   a

XXIIIa   XXIIIb

Analogously to the previously described syntheses, these heterocycles -- optionally under protection of the functional groups -- can be linked with vitamin D-aldehyde **VII**, whereby derivatives of general formula **II** with the corresponding heterocyclic substituents for Z' accumulate.

If aldehyde **IXX** is converted in a Wittig reaction into the corresponding vinyl compound, the 1,3-dipolar cycloadditions can also be carried out, which would then yield the corresponding

isoxazolines, pyrazolines or triazolines. Their treatment can be carried out analogously to the heteroaromatic derivatives.

It is also possible to convert carboxylic acid **VIII** or a corresponding derivative (ester, amide, acid chloride) under standard conditions (e.g., Claisen condensation) into 1,3-diketones of general formula **XXIV**.
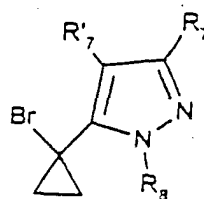

XXIV

Isoxazoles of general formula **XXV** can now be produced in the presence of hydroxylamine, and pyrazoles of general formula **XXVI** can be produced with hydrazines such as R_8-NH-NH$_2$.
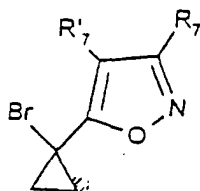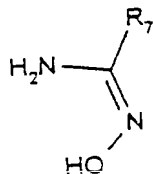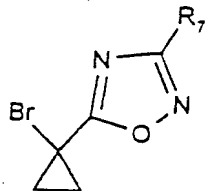

XXV   **XXVI**

Analogously to the previously described syntheses, these heterocycles -- optionally under protection of the functional groups -- can be linked with vitamin D-aldehyde **VII**, whereby derivatives of general formula **II** with the corresponding heterocyclic substituents accumulate.

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For synthesis of 1,2,4-oxadiazoles, derivatives of carboxylic acid **VIII** (acid chlorides, -esters, -orthoesters) can be reacted with amidoximes of general formula **XXVII**

XXVII

and thermally converted (optionally addition of trifluoroacetic acid anhydride) into 1,2,4-oxadiazoles of general formula **XXVIII** [L. B. Clapp **Adv. Heterocycl. Chem.** 20, 65 (1976)]. The formation of the 1,2,4-oxadiazoles can also be carried out under basic conditions (e.g., sodium methanolate).
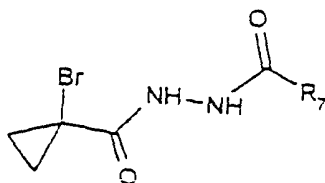

XXVIII

Analogously to the previously described syntheses, heterocycles of general formula **XXVIII** -- optionally under protection of the functional groups -- can be linked with the vitamin D-aldehyde **VII**, whereby derivatives of general formula II with the corresponding heterocyclic substituents accumulate.

Carboxylic acid derivatives (e.g., esters), which already have the calcitriol skeleton (DE 42 34 382), can also be converted directly into the corresponding 1,2,4-oxadiazoles.

For synthesis of 1,3,4-oxadiazoles, derivatives of carboxylic acid **VIII** can be converted into 1,2-diacylhydrazines of general formula **XXIX**

XXIX

which can be reacted thermally or under acid catalysis (e.g., acetic acid, hydrochloric acid, i.a.) to 1,3,4-oxazolines of general formula **XXX** (DE 28 08 842).
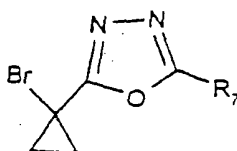

XXX

Analogously to the previously described syntheses, heterocycles of general formula **XXX** -- optionally under protection of functional groups -- can be linked with vitamin D-aldehyde **VII**, whereby derivatives of general formula **II** with the corresponding heterocyclic substituents accumulate.

The production of compounds that carry 6-membered rings at C-25 can be carried out quite analogously. For this purpose, the necessary reagents of general formula **XXXI** must be synthesized using known methods to create 6-ring-heterocycles (R. M. Acheson "An Introduction to the Chemistry of Heterocyclic Compounds,"

3rd Edition, John Wiley & Sons, New York, 1976, A. R. Katritzky,

J. M. Lagowsky "The Principles of Heterocyclic Chemistry,"

Chapman & Hall, London, 1971).
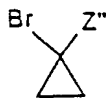
XXXI

Z" means pyridine, pyrazine, pyrimidine, pyridazine,

piperidine, tetrahydropyran rings, which can be substituted like

the 5-membered rings in one or more places with substituents such

as R_7.

Another general method of side chain introduction uses the

aldehyde of general formula **XXXII**,
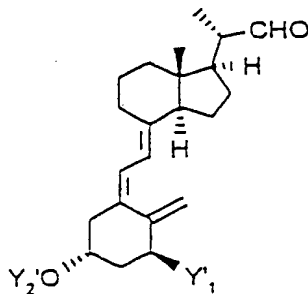
XXXII

which is accessible by photochemical isomerization of aldehyde

III (conditions analogous to reaction **V** reacted to **VI**).

Correspondingly, the isomerization as well as further reactions

also apply for aldehydes of general formula **IV**. By way of

example, however, only the further treatment of **XXXII** is cited.

The introduction of the side chain is carried out here by reaction with components of general formula **XXXIII**,
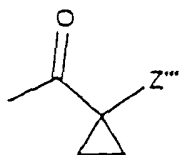
XXXIII

whereby Z''' can have all definitions that have already been given for Z, Z' and Z''. The synthesis of the corresponding components is possible according to standard methods. The linkage to aldehyde **XXXII** is carried out by deprotonation of ketone **XXXIII** with a base (e.g., lithium diisopropylamide, lithium-, sodium-, potassium hexamethyldisilazide, i.a.) in an aldol reaction, whereby derivatives of general formula **XXXIV** accumulate.
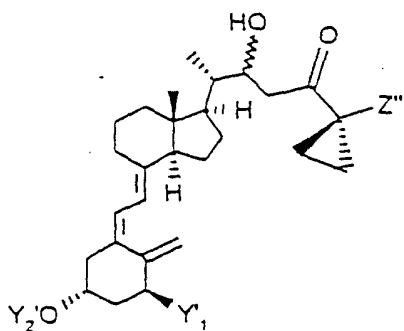
XXXIV

Conversion of the free hydroxy group into a leaving group (e.g., acetate, trifluoroacetate, methanesulfonate, toluenesulfonate, trifluoromethanesulfonate) and elimination

under basic conditions (e.g., diazabicycloundecane, diazabicyclononane, triethylamine, i.a.) then yields enone derivatives of general formula **XXXV**
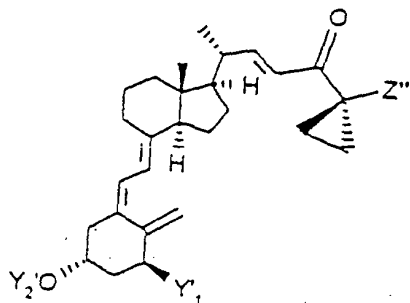
XXXV

Reduction of the keto groups with a reducing agent (e.g., sodium borohydride, sodium borohydride/cerium trichloride, lithium aluminum hydride, diisobutylaluminum hydride, i.a.) then results in derivatives of general formula II, for which the following applies: Q represents a hydroxymethyl group and Z''' is equal to Z', which are further reacted as described.

The production of compounds of general formula I, if R_1 and R_2 mean hydrogen atoms, is carried out in that a compound of general formula II',
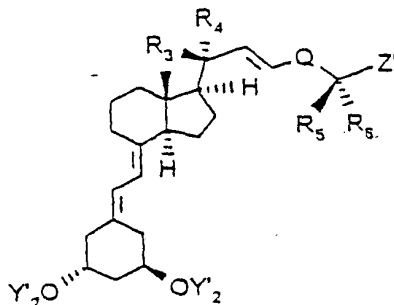
II'

whereby the already mentioned meanings exist for Y'_2, R_3, R_4, R_5, R_6, Q and Z', is treated analogously to the conditions that are described for the reaction of II.

The production of compounds of general formula II' is carried out in a convergent synthesis method, whereby CD and A-ring fragments are separately structured. Fo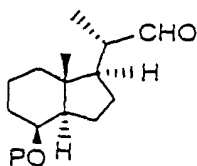r synthesis of the CD fragments, aldehyde XXXVI, known in the literature [H. H. Inhoffen et al. Chem. Ber. **91**, 780 (1958), Chem. Ber. **92**, 1772 (1959), W. G. Dauben **30** **Tetrahedron Lett.**, 677 (1989)] is used,

CHO
H
PO H

XXXVI

in which P means an acyl-, alkyl- or aryl-substituted silyl or tetrahydropyranyl, tetrahydrofuranyl, methoxymethyl, ethoxyethyl group or an acyl group (e.g., acetyl group, benzoyl group) or another alcohol protective group (see T. W. Greene, P. G. M. Wuts "Protective Groups in Organic Synthesis," 2nd Edition, John Wiley & Sons, Inc., 1991).

According to known processes, which have already been described for the normal series (see front and see also WO 94/07853), the corresponding side chains can also be built up on the CD fragment, whereby derivatives of general formula XXXVII

61

accumulate.
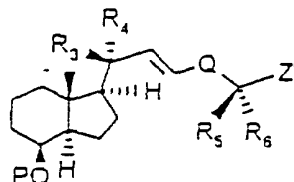
XXXVII

The radicals have been described previously. Protective group P is now removed by suitable reagents. For silyl protective groups, tetrabutylammonium fluoride, hydrofluoric acid or hydrofluoric acid/pyridine is used. In the case of the other ether groups, acids (e.g., p-toluenesulfonic acid, pyridinium-p-toluenesulfonate, acetic acid, oxalic acid, hydrochloric acid, phosphoric acid, acidic ion exchanger) are used. The acyl groups are cleaved under basic conditions (potassium carbonate, potassium hydroxide, sodium hydroxide, lithium hydroxide in alcohols, water, THF or corresponding solvent mixtures), whereby derivatives of general formula XXXVIII accumulate.
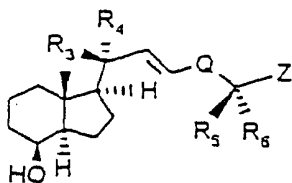
XXXVIII

The free hydroxy group is now converted with an oxidizing agent (pyridinium dichromate, pyridinium chlorochromate, barium manganate, Swern conditions, Dess-Martin reagent) into a ketone of general formula XXXIX.
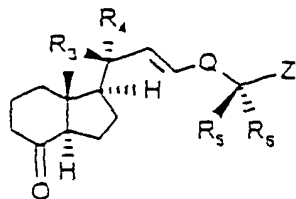
XXXIX

The compounds of general formula **XXXIX** are now converted by reaction with the anion of phosphine oxides of general formula **XL** produced by a base such as **n**-butyllithium or lithium diisopropylamine [H. F. DeLuca et al. **Tetrahedron Lett.** <u>32</u>, 7663 (1991)]
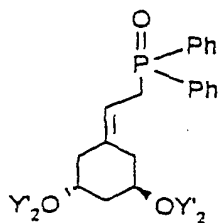
XL

into a compound of general formula **II'**.

For the synthesis of calcitriol derivatives of general formula **II** with 26,27-cyclomodification, which in addition have pyridyl substituents at C-25, the following synthesis method can be employed.

Carboxylic acid **VIII** is converted with pyridine thiol in the

presence of N,N'-dicyclohexylcarbodiimide into thioesters **XLI**,
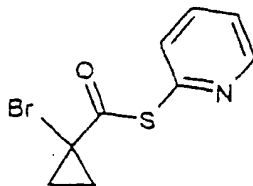
XLI

which are reacted with Grignard reagents such as **XLII** [Examples: D. Wenkert et al. **J. Org. Chem.** $\underline{50}$, 4114 (1985); S. Borelly, L. A. Paquette **J. Am. Chem. Soc.** $\underline{118}$, 727 (1996); T. E. Bellas **Tetrahedron** $\underline{25}$, 5149 (1969)]
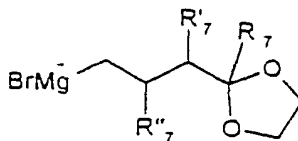
XLII

to ketones of general formula **XLIII**. For R''_7, the same definition applies as for R_7 and R'_7.
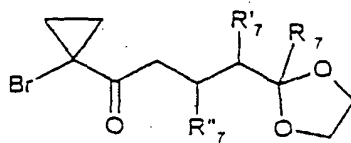
XLIII

The cyclization to pyridine derivatives of general formula **XLIV** can now be carried out under standard conditions (e.g., acetic acid, hydroxylamine hydrochloride) [G. Chelucci **Synth.**

Comm. **15**, 808 (1985)].
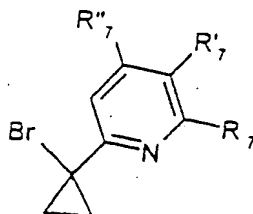
XLIV

The creation of the side chain is then carried out as in the case of oxazole derivatives by reaction of the cyclopropyl-metal compound that is generated by bromine-metal exchange and vitamin D-C-24 aldehyde **VII**, whereby derivatives of general formula **XLV** are obtained.
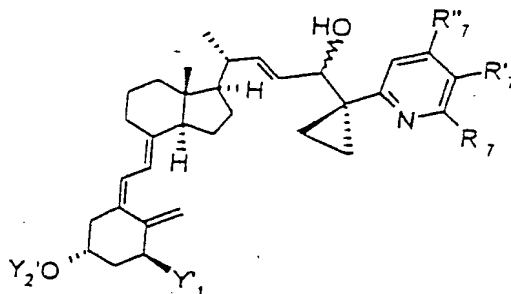
XLV

These can be regarded as special cases of general formula **II**, whose further reaction is already described.

For synthesis of calcitriol derivatives with 26,27-cyclomodification, which in addition has oxazoline substituents at C-25, the following synthesis method can be employed.

Carboxylic acid **VIII** is converted into the acid chloride of

general formula **XLVI**.
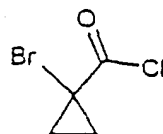
XLVI

The carboxylic acid can now be brought to reaction with amino alcohols of general formula **XLVII**,
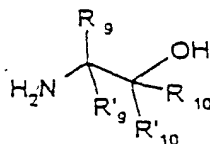
XLVII

whereby R_9, R'_9, R_{10}, and R'_{10}, independently of one another, mean a hydrogen atom, a straight-chain or branched, saturated or unsaturated cyclic (aromatic, aliphatic) alkyl radical with up to 12 carbon atoms, which can be interrupted at any point by oxa, thia or aza groups (substituted or unsubstituted) or by sulfoxide or sulfo groups or can carry other substituents (free or protected hydroxyl groups, halogen atoms).

In this case, amides of general formula **XLVIII** are produced,
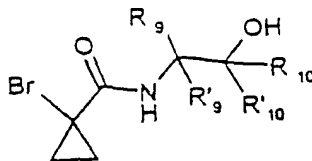
XLVIII

which are converted under standard conditions (e.g., phosphorus oxychloride) into the oxazolines of general formula **XLIX** [N. Langlois et al. **Heterocycles** _42_, 635 (1996)].
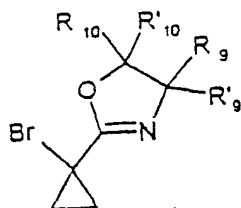
XLIX

The creation of the side chain is then carried out as in the case of the oxazole derivatives by reaction of the cyclopropyl-metal compound that is generated by bromine-metal exchange and the vitamin D-C-24-aldehyde **VII**, whereby derivatives of general formula **L** are obtained.
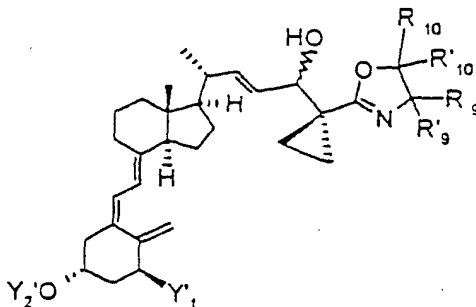
L

These can be regarded as special cases of general formula II, whose further reaction is already described.

The invention thus also contains intermediate products of general formulas **XI**, **XII** and **XLIV** within the production of

vitamin D derivatives according to the invention
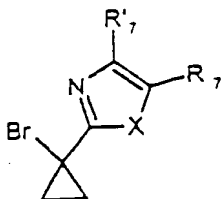
XI X=O
XIII X=S
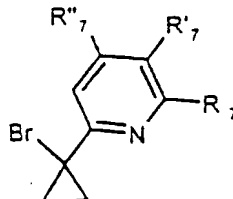
XLIV

in which R_7, R'_7 and R''_7, independently of one another, mean a hydrogen atom, a straight-chain or branched, saturated or unsaturated alkyl radical with up to 12 carbon atoms, which at any points can be interrupted by oxa, thia or aza groups (substituted or unsubstituted) or sulfoxide or sulfo groups or can carry other substituents (free or protected hydroxy groups, halogen atoms).

The following examples are used for a more detailed explanation of the invention.

Synthesis of the Starting Compounds in the 5-Alkyloxazole Series
(5Z,7E,22E)-(1S,3R)-1,3-Bis[[dimethyl(1,1-dimethylethyl)-
silyl]oxy]-9,10-secochola-5,7,10(19),22-tetraen-24-al **3**

a) An amount of 1.40 g of (5E,7E,22E)-(1S,3R)-1,3-
bis[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-N-methyl-N-methoxy-
9,10-secochola-5,7,10(19),22-tetraen-24-amide **1** (WO 94/07853) is
dissolved in 200 ml of toluene, and after 232 mg of anthracene
and 4 drops of triethylamine are added, it is irradiated through
Pyrex glass with a high-pressure mercury-vapor lamp (Heraeus TQ
150) for 12 minutes under nitrogen. Then, it is filtered and
concentrated by evaporation. After this procedure is performed
several times (11 times), 11.4 g of (5Z,7E,22E)-(1S,3R)-1,3-
bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-N-methyl-N-methoxy-
9,10-secochola-5,7,10(19),22-tetraene-24-amide **2** is obtained as a
yellow oil.

b) 7.8 g of amide **2** is dissolved in 39.15 ml of THF and
treated drop by drop at -78°C with 49.62 ml of diisobutylaluminum
hydride (1.2 M in toluene). After 70 minutes, 2.84 ml of
methanol is added at -78°C, and then the reaction mixture is
stirred into ice-cold sodium tartrate solution and stirred
thoroughly with 370 ml of diethyl ether for 1.5 hours. The ether
phase is concentrated by evaporation and chromatographed on
silica gel with ethyl acetate/hexane, whereby 5.44 g of title
compound **3** accumulates as a yellow, resin-like material.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.08 ppm (s, 12H); 0.58 (s,
3H); 0.88 (s, 18H); 1.17 (d, 3H); 4.20 (m, 1H); 4.38 (m, 1H);

4.85 (brs, 1H); 5.18 (brs, 1H); 6.02 (d, 1H); 6.08 (dd, 1H); 6.23 (d, 1H); 6.72 (dd, 1H); 9.48 (d, 1H)

2-(1-Bromocyclopropyl)-5-propyloxazole __7__

a) A mixture of 2.57 g of 1-bromocyclopropanecarboxylic acid __4__ [H. M. R. Hoffmann et al. **J. Org. Chem.** __54__, 6096 (1989)], 2.22 g of 1-amino-2-pentanone hydrochloride __5__ [M. Jackman et al. **J. Am. Chem. Soc.** __70__, 2884 (1948)] and 3.36 g of N,N'-dicyclohexylcarbodiimide in 234 ml of methylene chloride in the presence of 2.46 ml of triethylamine is stirred overnight at room temperature. Then, it is filtered, the filtrate is concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane. 2.74 g of 1-bromo-N-(2-oxopentyl)-cyclopropane-1-carbamide __6__ is obtained as a crystallizing oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.92 pm (t, 3H); 1.32 (m, 2H); 1.68 (m, 4H); 2.45 (t, 2H); 4.12 (d, 2H); 7.58 (brs, 1H)

Obtained analogously are:

1-Bromo-N-(2-oxopropyl)-cyclopropane-1-carbamide from 1-amino-2-propanone hydrochloride [J. D. Hepworth **Org. Synth.** __45__, 1 (1965)

1-bromo-N-(2-oxobutyl)-cyclopropane-1-carbamide from 1-amino-2-butanone hydrochloride [M. Jackman et al. **J. Am. Chem. Soc.** __70__, 2884 (1948)]

1-bromo-N-(2-oxoheptyl)-cyclopropane-1-carbamide from 1-amino-2-heptanone hydrochloride [M. Jackman et al. **J. Am. Chem. Soc.** __70__, 2884 (1948)]

b)   2.14 g of <u>6</u> and 6.42 g of polyphosphoric acid are held
at 140°C for 3.5 hours. The reaction mixture is then mixed with
ice/sodium carbonate solution and extracted with ethyl acetate.
After drying on sodium sulfate, it is chromatographed on silica
gel with ethyl acetate/hexane. 1.47 g of title compound <u>7</u> is
obtained as a yellow oil.

   ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.98 ppm (t, 3H); 1.50 (m,
2H); 1.60 (m, 4H); 2.59 (t, 2H); 6.65 (s, 1H)

2-(1-Bromocyclopropyl)-5-methyloxazole <u>8</u>

   4.62 g of 1-bromo-N-(2-oxopropyl)-cyclopropane-1-carbamide
is held at 60°C in 35.47 ml of concentrated sulfuric acid for 30
minutes. The cooled reaction mixture is stirred into ice water
and made basic in batches with sodium carbonate decahydrate.
Then, it is extracted with ethyl acetate, dried on sodium
sulfate, and concentrated by evaporation. Chromatography of the
oily residue on silica gel with ethyl acetate/hexane yields 2.79
g of title compound <u>8</u> as a yellowish oil.

   ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.50 ppm (m, 2H); 1.60 (m,
2H); 2.30 (s, 3H); 6.65 (s, 1H)

   Obtained analogously are:

   2-(1-Bromocyclopropyl)-5-ethyloxazole <u>9</u> from 1-bromo-N-(2-
oxobutyl)-cyclopropane-1-carbamide

   ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.24 ppm (t, 3H); 1.50 (m,
2H); 1.60 (m, 2H); 2.65 (q, 2H); 6.65 (s, 1H)

2-(1-bromocyclopropyl)-5-pentyloxazole 10 from 1-bromo-N-(2-oxoheptyl)-cyclopropane-1-carbamide

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.90 ppm (t, 3H); 1.33 (m, 4H); 1.50 (m, 2H); 2.60 (t, 2H); 6.65 (s, 1H)

Example 1

(5Z,7E,22E)-(1S,3R,24S)-25-(5-Propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol 12a and

(5Z,7E,22E)-(1S,3R,24S)-25-(5-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol 12b

1.0 g of 2-(1-bromocyclopropyl)-5-propyloxazole 7 in 2.0 ml of diethyl ether is added drop by drop at -78°C to 4.78 ml of tert-butyllithium (1.7 M in pentane) in 13.6 ml of diethyl ether. After 5 minutes, 869 mg of 3 in 5.44 ml of diethyl ether is added in drops. After 10 minutes, the reaction mixture is allowed to reach 0°C and then stirred into saturated ammonium chloride solution. After extraction with diethyl ether and drying on sodium sulfate, 1.58 g of yellow oil is obtained. By chromatography on silica gel with ethyl acetate/hexane, 420 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis[[dimethyl(1,1-dimethyl-ethyl)silyl]oxy]-25-(5-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol 11a and 380 mg of (5Z,7E,22E)-(1S,3R,24R)-1,3-bis[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-25-(5-propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol 11b are obtained in the elution sequence as oils.

410 mg of **11a** is allowed to stand in 15.9 ml of THF with 841 mg of tetrabutylammonium fluoride (trihydrate) overnight at room temperature. Then, another 420 mg of tetrabutylammonium fluoride (trihydrate) is added, and it is stirred for 5 hours. After saturated sodium bicarbonate solution and saturated sodium chloride solution are added, it is extracted with ethyl acetate. After the organic phase is dried with sodium sulfate, it is concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane. 110 mg of title compound **12a** is obtained as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.57 ppm (s, 3H); 1.00 (m, 8H); 1.15 (m, 2H); 2.55 (t, 2H); 4.12 (d, 2H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.42 (dd, 1H); 5.58 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.58 (s, 1H)

Analogously, title compound **12b** is obtained from **11b** with tetrabutylammonium fluoride (trihydrate) as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.57 ppm (s, 3H); 1.00 (m, 8H); 1.15 (m, 2H); 2.55 (t, 2H); 4.12 (d, 2H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.42 (dd, 1H); 5.53 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.58 (s, 1H)

Example 2

(5Z,7E,22E)-(1S,3R,24R)-25-(5-Methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **13b**

Analogously to Example 1, starting from aldehyde **3**, title compound **13b** is obtained as a colorless foam with 2-(1-bromocyclopropyl)-5-methyloxazole **8**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.57 ppm (s, 3H); 0.97 (m, 2H); 1.05 (m, 3H); 1.15 (m, 2H); 2.24 (s, 2H); 4.10 (d, 2H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.42 (dd, 1H); 5.53 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.58 (s, 1H)

Example 3

(5Z,7E,22E)-(1S,3R,24R)-25-(5-Ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **14b**

Analogously to Example 1, starting from aldehyde **3**, title compound **14b** is obtained as a colorless foam with 2-(1-bromocyclopropyl)-5-ethyloxazole **9**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.57 ppm (s, 3H); 0.97 (m, 2H); 1.05 (m, 3H); 1.20 (m, 5H); 2.60 (q, 3H); 4.12 (d, 2H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.42 (dd, 1H); 5.53 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.58 (s, 1H)

Example 4

(5Z,7E,22E)-(1S,3R,24R)-25-(5-Pentyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **15b**

Analogously to Example 1, starting from aldehyde **3**, title compound **15b** is obtained as a colorless foam with 2-(1-bromocyclopropyl)-5-pentyloxazole **10**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.57 ppm (s, 3H); 0.90 (t, 3H); 1.05 (m, 3H); 1.15 (m, 2H); 2.55 (s, 3H); 4.12 (d, 2H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.42 (dd, 1H); 5.53 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.60 (s, 1H)

Synthesis of the Starting Materials in the 4-Alkylthiazole Series

2-(1-Bromocyclopropyl)-4-ethylthiazole **17**

10.0 g of 1-bromopropanecarboxylic acid in **4**, and 173 ml of methylene chloride are stirred with 8.36 g of N-hydroxysuccinimide for 10 minutes at room temperature under nitrogen. At 0°C, 15.0 g of N,N-dicyclohexylcarbodiimide is added, and it is stirred for 3 hours at 0°C. Then, 10.0 ml of a 33% aqueous ammonia solution is added, and it is stirred for another 3 hours at 0°C. The reaction mixture is filtered, the filtrate is concentrated by evaporation, and the residue (14.12 g of colorless solid) is chromatographed on silica gel with ethyl acetate/hexane. 9.01 g of 1-bromocyclopropanecarboxylic acid amide **16** is obtained as a colorless solid (flash point 104-107°C).

4.64 g of **16** in 2.0 ml of toluene is stirred with 1.11 g of phosphorus pentasulfide and 4.17 g of 1-bromo-2-butanone (from 2-butanone and bromine in the presence of methanol) for 13 minutes at 50°C. The cooled reaction mixture is mixed with ice and 100 ml of saturated sodium bicarbonate solution. Then, it is extracted with ethyl acetate, and the organic phase is dried with sodium sulfate. After the solvent is removed, the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 810 mg of title compound **17** accumulates as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.25 ppm (t, 3H); 1.60 (m, 2H); 1.75 (m, 2H); 2.72 (q, 2H); 6.78 (s, 1H)

Obtained analogously are:

2-(1-Bromocyclopropyl)-4-methylthiazole __18__ from

chloroacetone at 100°C and a reaction time of 30 minutes.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.60 ppm (m, 2H); 1.75 (m,

2H); 2.38 (s, 3H); 6.78 (s, 1H)

2-(1-Bromocyclopropyl)-4-propylthiazole __19__ from 1-

bromopentanone at 50°C and a reaction time of 20 minutes.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.95 ppm (t, 3H); 1.60 (m,

2H); 1.69 (m, 2H); 1.75 (m, 2H); 2.65 (t, 2H); 6.78 (s, 1H)

2-(1-Bromocyclopropyl)-4-butylthiazole __20__ from 1-bromo-2-

hexanone at 100°C and a reaction time of 2 minutes.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.95 ppm (t, 3H); 1.38 (m,

2H); 1.60 (m, 2H); 1.75 (m, 2H); 2.68 (t, 2H); 6.78 (s, 1H)

Example 5

(5Z,7E,22E)-(1S,3R,24S)-25-(4-Ethylthiazol-2-yl)-26,27-cyclo-

9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol __22a__ and

(5Z,7E,22E)-(1S,3R,24R)-25-(4-ethylthiazol-2-yl)-26,27-cyclo-

9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol __22b__

2.94 ml of **tert**-butyllithium (1.7 M in pentane) is added at

-20°C under nitrogen to 8 ml of Trapp mixture (THF, ether,

pentane = 4:1:1) and cooled to -116°C (ether, liquid nitrogen).

Then, 580 mg of __17__ is added in drops to 1 ml of Trapp mixture,

and it is stirred for 1 hour at -116°C. Then, 950 mg of aldehyde

__3__ is added in drops to 1 ml of Trapp mixture. After 30 minutes

at this temperature, saturated ammonium chloride solution is added and extracted with ethyl acetate. After the organic phase is dried on sodium sulfate and after the solvent is concentrated by evaporation, a residue of 890 mg is obtained as a yellow oil. By chromatography on silica gel with ethyl acetate/hexane, 210 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-ethyl-thiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **21a** and 200 mg of (5Z,7E,22E)-(1S,3R,24R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-ethylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **21b** are obtained in the elution sequence as light yellow oils.

210 mg of **21a** is dissolved in 7 ml of THF and allowed to stand with 420 mg of tetrabutylammonium fluoride (trihydrate) overnight at room temperature under nitrogen. Then, it is poured into a mixture of saturated sodium chloride and saturated sodium bicarbonate solution (50:1), extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 56 mg of title compound **22a** is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.50 ppm (s, 3H); 0.98 (d, 3H); 1.05 (m, 4H); 1.25 (t, 3H); 2.74 (q, 2H); 3.97 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.40 (dd, 1H); 5.56 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.65 (s, 1H)

Analogously, from **21b**, title compound **22b** is obtained as a colorless foam with tetrabutylammonium fluoride (trihydrate).

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 0.98 (d, 3H); 1.05 (m, 4H); 1.25 (t, 3H); 2.74 (q, 2H); 3.98 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.38 (dd, 1H); 5.51 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.65 (s, 1H)

Example 6

(5Z,7E,22E)-(1S,3R,24R)-25-(4-Methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **23b**

Analogously to Example 5, starting from aldehyde **3**, title compound **23b** is obtained as a colorless foam with 2-(1-bromocyclopropyl)-4-methylthiazole **18**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 1.00 (d, 3H); 1.05 (m, 4H); 2.40 (s, 3H); 3.98 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.38 (dd, 1H); 5.51 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.65 (s, 1H)

Example 7

(5Z,7E,22E)-(1S,3R,24R)-25-(4-Propylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **24b**

Analogously to Example 5, starting from aldehyde **3**, title compound **24b** is obtained as a colorless foam with 2-(1-bromocyclopropyl)-4-propylthiazole **19**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 0.98 (m, 7H); 1.05 (m, 4H); 2.68 (t, 2H); 3.98 (d, 1H); 4.23 (m, 1H); 4.43

(m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.38 (dd, 1H); 5.50 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.65 (s, 1H)

Example 8

(5Z,7E,22E)-(1S,3R,24R)-25-(4-Butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **25b**

Analogously to Example 5, starting from aldehyde **3**, title compound **25b** is obtained as a colorless foam with 2-(1-bromocyclopropyl)-4-butylthiazole **20**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 0.92 (t, 3H); 0.98 (d, 3H); 1.05 (m, 4H); 2.69 (t, 2H); 3.98 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.38 (dd, 1H); 5.50 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.65 (s, 1H)

Synthesis of Starting Materials in the Phenyl Series

1-(Phenylcyclopropan-1-yl)-1-ethanone **28**

4.5 g of 1-phenyl-1-cyclopropanecarboxylic acid **26** in 80 ml of methylene chloride is stirred with 3.83 g of N-hydroxysuccinimide for 10 minutes at room temperature under nitrogen. At 0°C, 6.84 g of N,N'-dicyclohexylcarbodiimide is added, and it is stirred for 1.5 more hours. Then, 7.74 ml of an aqueous dimethylamine solution is added, and it is stirred for another 30 minutes at 0°C and for 12 hours at room temperature. It is concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 4.34 g of 1-phenyl-1-cyclopropanecarboxylic acid-dimethylamide **27** accumulates as a crystallizing oil.

4.34 g of <u>27</u> is dissolved in 189 ml of THF, cooled to -10°C, and 21.5 ml of methyllithium solution (1.6 M in diethyl ether) is added in drops under nitrogen. It is stirred for 2 hours at this temperature, and the reaction mixture is then poured into saturated ammonium chloride solution. After extraction with ethyl acetate, the organic phase is dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 3.7 g of title compound <u>28</u> is obtained as a yellowish oil.

(5Z,7E)-(1S,3R)-1,3-Bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-9,10-secopregna-5,7,10(19)-triene-20-carbaldehyde <u>30</u>

7.5 g of (5E,7E)-(1S,3R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-9,10-seco-pregna-5,7,10(19)-triene-20-carbaldehyde <u>29</u> [M. J. Calverley **Tetrahedron** <u>43</u>, 4609 (1987)] is dissolved in 200 ml of toluene, 2 g of anthracene and 0.5 ml of triethylamine are added and irradiated while nitrogen is passing through it in a Pyrex apparatus with a high-pressure mercury-vapor lamp for 30 minutes. Then, it is filtered, concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby title compound <u>30</u> is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.05 ppm (s, 12H); 0.55 (s, 3H); 0.88 (s, 18H); 1.11 (d, 3H); 2.37 (m, 1H); 4.18 (m, 1H); 4.37 (m, 1H); 4.84 (brs, 1H); 5.17 (brs, 1H); 6.00 (d, 1H); 6.22 (d, 1H)

Example 9

(5Z,7E,22E)-(1S,3R,24S)-25-Phenyl-26,27-cyclo-9,10-secocholesta-
5,7,10(19),22-tetraene-1,3,24-triol **35a** and (5Z,7E,22E)-
(1S,3R,24R)-25-phenyl-26,27-cyclo-9,10-secocholesta-
5,7,10(19),22-tetraene-1,3,24-triol **35b**

17.4 ml of **n**-butyllithium solution (1.6 M in hexane) is
added in drops at 0°C to 3.86 ml of diisopropylamine in 20.7 ml
of THF under nitrogen. It is stirred for 20 minutes at this
temperature, cooled to -78°C and then 4.42 g of ketone **28** is
added in drops to 6.2 ml of THF. After 1 hour at -78°C, 2.3 g of
aldehyde **30** is added to 18.8 ml of THF, and it is stirred for 1
more hour. The reaction mixture is then stirred into ice-cold
ammonium chloride solution and extracted with ethyl acetate.
After the organic phase is dried on sodium sulfate, the solvent
is removed and chromatographed on silica gel with ethyl
acetate/hexane, whereby 1.57 g of (5Z,7E)-(1S,3R)-1,3-
bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-22-hydroxy-25-phenyl-
26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-one **31** is
obtained as a colorless foam.

1.57 g of **31** is dissolved in 6.3 ml of pyridine, mixed with
2.08 ml of acetic anhydride and stirred overnight under nitrogen
at room temperature. Then, the reaction mixture is mixed with
aqueous oxalic acid (5%) and extracted with ethyl acetate. After
the organic phase is dried on sodium sulfate and after
chromatography on silica gel with ethyl acetate/hexane, 1.44 g of
(5Z,7E)-(1S,3R)-22-(acetyloxy)-1,3-bis[[dimethyl(1,1-

dimethylethyl)silyl]oxy]-25-phenyl-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-one **32** is obtained as a colorless foam.

1.44 g of **32** is dissolved in 40 ml of toluene and stirred with 8.13 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 30 minutes at 40°C under nitrogen. The reaction mixture is diluted with 150 ml of ethyl acetate and stirred into 600 ml of 0.01N hydrochloric acid. It is extracted with ethyl acetate, dried on sodium sulfate, and the solvent is removed, whereby 1.31 g of (5Z,7E,22E)-(1S,3R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-phenyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-one **33** is obtained as a colorless oil.

1.31 g of enone **33** is dissolved in 3.1 ml of THF and 7.2 ml of methanol and mixed at 0°C under nitrogen with 7.2 ml of a 0.4 molar methanolic cerium trichloride-heptahydrate solution. Then, 200 mg of sodium borohydride is added in portions and stirred for 40 more minutes at 0°C. Ice water is now added, extracted with ethyl acetate and dried on sodium sulfate. The residue is chromatographed on silica gel with hexane/ethyl acetate, whereby in the elution sequence, 133 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-phenyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **34a** and 374 mg of (5Z,7E,22E)-(1S,3R,24R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-phenyl-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **34b** accumulate as colorless foams.

133 mg of **34a** is allowed to stand in 5.6 ml of THF with 295 mg of tetrabutylammonium fluoride (trihydrate) overnight at room temperature under nitrogen. The reaction mixture is then stirred

into ice-cold saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic phases are washed with water, dried on sodium sulfate and concentrated by evaporation. Chromatography of the residue on silica gel with ethyl acetate/hexane yields 38 mg of title compound **35a** as a colorless foam.

^{1}H-NMR (300 MHz, CDCl_3): δ = 0.57 ppm (s, 3H); 0.85 (m, 4H); 1.05 (d, 3H); 3.78 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.30 (dd, 1H); 5.32 (brs, 1H); 5.42 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 7.30 (m, 5H)

Analogously to **34a**, title compound **35b** is obtained as a colorless foam from **34b**.

^{1}H-NMR (300 MHz, CDCl_3): δ = 0.57 ppm (s, 3H); 0.85 (m, 4H); 1.00 (d, 3H); 3.70 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.30 (dd, 1H); 5.32 (brs, 1H); 5.42 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 7.30 (m, 5H)

Synthesis of the Starting Materials in the 4-Alkyl-Phenyl Series
4-Methylbenzene acetaldehyde **37**

28.5 g of methoxymethyltriphenylphosphonium chloride is introduced into 350 ml of diethyl ether under nitrogen. At 0°C, 39.95 ml of n-butyllithium solution (1.6 M in hexane) is added in drops, and it is stirred for one hour at room temperature. 10 g of 4-methylbenzaldehyde in 50 ml of diethyl ether is now added, and it is stirred for one more hour. Sodium chloride solution is added to the reaction mixture, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. After

chromatography on silica gel with ethyl acetate/hexane, 7.8 g of 1-methoxy-2-(4-methylphenyl)-ethene **36** (E,Z-mixture) is obtained as a colorless oil, which is dissolved in 200 ml of acetone and is stirred overnight under nitrogen with 10 ml of 2N hydrochloric acid. Sodium chloride solution is added, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. Chromatographic purification on silica gel with ethyl acetate/hexane yields 4.5 g of title compound **37** as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.38 ppm (s, 3H); 3.68 (d, 2H); 7.12 (d, 2H); 7.22 (d, 2H); 9.74 (t, 1H)

2-(4-Methylphenyl)-2-propenal **38**

2.57 g of aldehyde **37** is introduced into 300 ml of methylene chloride under nitrogen, and 6.5 ml of triethylamine and 7.1 g of Eschenmoser's salt are added at 0°C. After 2.5 hours at 0°C, saturated ammonium chloride solution is added, extracted with methylene chloride, washed with sodium chloride solution, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 1.94 g of title compound **38** accumulates as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.39 ppm (s, 3H); 6.17 (s, 1H); 6.62 (s, 1H); 7.22 (d, 2H); 7.39 (d, 2H); 9.82 (s, 1H)

3-(4-Methylphenyl)-3-buten-2-ol **39**

2.34 g of aldehyde **38** is dissolved in 150 ml of diethyl ether and cooled to -78°C under nitrogen. 20 ml of methyllithium solution (1.6 M in diethyl ether) is now added in drops. After 1.5 hours at this temperature, it is quenched with saturated ammonium chloride solution, extracted with ethyl acetate, washed with sodium chloride solution, dried on sodium sulfate, and the solvent is removed. The residue is purified by chromatography on silica gel with ethyl acetate/hexane, whereby in addition to 237 mg of starting material, 1.06 g of title compound **39** accumulates as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 2.38 ppm (s, 3H); 1.35 (d, 3H); 4.82 (q, 1H); 5.28 (s, 1H); 5.34 (s, 1H); 7.18 (d, 2H); 7.32 (d, 2H)

3-(4-Methylphenyl)-3-buten-2-one **40**

2.91 g of alcohol **39** is dissolved in 300 ml of methylene chloride, and 43.5 g of manganese dioxide is added under nitrogen. It is stirred overnight at room temperature, filtered on Celite, and the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 850 mg of title compound **40** in addition to 1.06 g of the starting material are obtained as colorless oils.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 2.45 ppm (s, 3H); 2.60 (s, 3H); 5.94 (s, 1H); 6.12 (s, 1H); 7.28 (d, 2H); 7.88 (d, 2H)

1-[1-(4-Methylphenyl)cyclopropyl]ethanone **41**

507 mg of sodium hydride (55% in paraffin oil) is introduced into 20 ml of dimethylformamide under nitrogen at 0°C, and 1.36 g of trimethylsulfonium iodide is added. After 30 minutes at this temperature, 845 mg of ketone **40** is added in drops to 4 ml of dimethylformamide. It is stirred for 1 more hour at 0°C, then quenched with sodium chloride solution, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. After chromatography on silica gel with ethyl acetate/hexane, 447 mg of title compound **41** is obtained as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.14 ppm (m, 2H); 1.59 (m, 2H); 2.01 (s, 3H); 2.38 (s, 3H); 7.28 (d, 2H); 7.88 (d, 2H)

4-(1-Methylethyl)benzene acetaldehyde **43**

27.7 g of methoxymethyltriphenylphosphonium chloride is introduced into 350 ml of diethyl ether under nitrogen. At 0°C, 38.8 ml of n-butyllithium solution (1.6 M in hexane) is added in drops, and it is stirred for one hour at room temperature. 12 g of 4-isopropylbenzaldehyde in 50 ml of diethyl ether is now added, and it is stirred for one more hour. Sodium chloride solution is added to the reaction mixture, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. After chromatography on silica gel with ethyl acetate/hexane, 8.1 g of 1-methoxy-2-[4-(1-methylethyl)phenyl]-ethene **42** (E, Z-mixture) is obtained as a colorless oil, which is dissolved in 200 ml of acetone and stirred under nitrogen with 10 ml of 2N hydrochloric acid overnight. Sodium chloride solution is added,

extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. Chromatographic purification on silica gel with ethyl acetate/hexane yields 5.1 g of title compound **43** as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.28 ppm (d, 6H); 2.92 (hept, 1H); 3.68 (d, 2H); 7.16 (d, 2H); 7.24 (d, 2H); 9.73 (t, 1H)

2-[4-(1-Methylethyl)phenyl]-2-propenal **44**

4.65 g of aldehyde **43** is introduced into 300 ml of methylene chloride under nitrogen, and 7.9 ml of triethylamine and 6.9 g of Eschenmoser's salt are added at 0°C. After 2.5 hours at 0°C, saturated ammonium chloride solution is added, extracted with methylene chloride, washed with socium chloride solution, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 3.84 g of title compound **44** accumulates as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.28 ppm (d, 6H); 2.93 (hept, 1H); 6.15 (s, 1H); 6.62 (s, 1H); 7.26 (d, 2H); 7.41 (d, 2H); 9.81 (s, 1H)

3-[4-(1-Methylethyl)phenyl]-3-buten-2-ol **45**

6.1 g of aldehyde **44** is dissolved in 250 ml of diethyl ether and cooled under nitrogen to -78°C. 35.8 ml of a methllithium solution (1.6 M in diethyl ether) is now added in drops. After 1.5 hours at this temperature, it is quenched with saturated ammonium chloride solution, extracted with ethyl acetate, washed

with sodium chloride solution, dried on sodium sulfate, and the solvent is removed. The residue is purified by chromatography on silica gel with ethyl acetate/hexane, whereby 2.8 g of title compound **45** accumulates as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.27 ppm (d, 6H); 2.92 (hept, 1H); 1.33 (d, 3H); 4.83 (q, 1H); 5.29 (s, 1H); 5.34 (s, 1H); 7.20 (d, 2H); 7.34 (d, 2H)

3-[4-(1-Methylethyl)phenyl]-3-buten-2-one **46**

2.75 g of alcohol **45** is dissolved in 300 ml of methylene chloride, and 25.1 g of manganese dioxide is added under nitrogen. It is stirred overnight at room temperature, filtered on Celite, and the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 937 mg of title compound **46** in addition to 635 mg of the starting material is obtained as colorless oils.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.28 ppm (d, 6H); 2.46 (s, 3H); 2.93 (hept, 1H); 5.97 (s, 1H); 6.14 (s, 1H); 7.33 (d, 2H); 7.98 (d, 2H)

1-[1-[4-(1-Methylethyl)phenyl]cyclopropyl]ethanone **47**

474 mg of sodium hydride (55% in paraffin oil) is introduced into 20 ml of dimethylformamide under nitrogen at 0°C, and 1.29 g of trimethylsulfonium iodide is added. After 30 minutes at this temperature, 930 mg of ketone **46** is added in drops to 4 ml of dimethylformamide. It is stirred for 1 more hour at 0°C, then quenched with sodium chloride solution, extracted with ethyl

acetate, dried on sodium sulfate and concentrated by evaporation. After chromatography on silica gel with ethyl acetate/hexane, 447 mg of title compound **47** is obtained as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.18 ppm (m, 2H); 1.28 (d, 6H); 1.60 (m, 2H); 2.92 (hept, 1H); 2.02 (s, 3H); 7.20 (d, 2H); 7.30 (d, 2H)

4-Butylbenzene acetaldehyde **49**

21.1 g of methoxymethyltriphnylphosphonium chloride is introduced into 280 ml of diethyl ether under nitrogen. At 0°C, 29.6 ml of n-butyllithium solution (1.6 M in hexane) is added in drops, and it is stirred for one hour at room temperature. 10 g of 4-butylbenzaldehyde in 40 ml of diethyl ether is now added, and it is stirred for one more hour. Sodium chloride solution is added to the reaction mixture, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. After chromatography on silica gel with ethyl acetate, 6.7 g of 2-(4-butylphenyl)-1-methoxyethene **48** (E,Z-mixture) is obtained as a colorless oil, which is dissolved in 200 ml of acetone and is stirred under nitrogen with 10 ml of 2N hydrochloric acid overnight. Sodium chloride solution is added, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. Chromatographic purification on silica gel with ethyl acetate/hexane yields 3.9 g of title compound **49** as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.95 ppm (t, 3H); 1.37 (m, 2H); 1.62 (m, 2H); 3.68 (d, 2H); 7.14 (d, 2H); 7.20 (d, 2H); 9.74 (t, 1H)

3-(4-Butylphenyl)-3-buten-2-ol **51**

3.86 g of aldehyde **43** is introduced into 300 ml of methylene chloride under nitrogen, and 6.0 ml of triethylamine and 5.3 g of Eschenmoser's salt are added at 0°C. After 2.5 hours at 0°C, saturated ammonium chloride solution is added, extracted with methylene chloride, washed with sodium chloride solution, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 3.24 g of 2-(4-butylphenyl)-2-propen-1-al **50** accumulates as a colorless oil, which is dissolved in 200 ml of diethyl ether and cooled under nitrogen to -78°C. 27.4 ml of a methyllithium solution (1.6 M in diethyl ether) is now added in drops. After 1.5 hours at this temperature, it is quenched with saturated ammonium chloride solution, extracted with ethyl acetate, washed with sodium chloride solution, dried on sodium sulfate, and the solvent is removed. The residue is purified by chromatography on silica gel with ethyl acetate/hexane, whereby 1.8 g of title compound **51** accumulates as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.97 ppm (t, 3H); 1.35 (d, 3H); 1.61 (m, 4H); 2.62 (t, 2H); 4.83 (q, 1H); 5.29 (s, 1H); 5.34 (s, 1H); 7.18 (d, 2H); 7.33 (d, 2H)

3-(4-Butylphenyl)-3-buten-2-one **52**

1.07 g of alcohol **51** is dissolved in 100 ml of methylene chloride, and 9.1 g of manganese dioxide is added under nitrogen. It is stirred overnight at room temperature, filtered on Celite and the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 301 mg of title compound **52** in addition to 395 mg of the starting material are obtained as colorless oils.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.95 ppm (t, 3H); 1.37 (m, 2H); 1.60 (m, 2H); 2.43 (s, 3H); 2.65 (t, 2H); 5.94 (s, 1H); 6.12 (s, 1H); 7.18 (d, 2H); 7.22 (d, 2H)

1-[1-(4-Butylphenyl)cyclopropyl]ethanone **53**

507 mg of sodium hydride (55% in paraffin oil) is introduced into 20 ml of dimethylformamide under nitrogen at 0°C, and 1.38 g of trimethylsulfonium iodide is added. After 30 minutes at this temperature, 1.06 g of ketone **52** is added in drops to 4 ml of dimethylformamide. It is stirred for 1 more hour at 0°C, then quenched with sodium chloride solution, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. After chromatography on silica gel with ethyl acetate/hexane, 702 mg of title compound **53** is obtained as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.96 ppm (m, 2H); 1.17 (m, 2H); 1.37 (hex, 2); 1.59 (m, 2H); 1.60 (m, 2H); 2.64 (t, 2H); 2.02 (s, 3H); 7.17 (d, 2H); 7.29 (d, 2H)

Example 10

(5Z,7E)-(1S,3R,24R)-25-(4-Methylphenyl)-26,27-cyclo-9,10-
secocholesta-5,7,10(19),20(22)-tetraene-1,3,24-triol **59b**,

(5Z,7E,22E)-(1S,3R,24S)-25-(4-methylphenyl)-26,27-cyclo-9,10-
secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **60a** and

(5Z,7E,22E)-(1S,3R,24R)-25-(4-methylphenyl)-26,27-cyclo-9,10-
secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **60b**

1.01 ml of n-butyllithium solution (1.6 M in hexane) is
added in drops at 0°C to 0.33 ml of diisopropylamine in 10 ml of
THF under nitrogen. It is stirred for 20 minutes at this
temperature, cooled to -78°C, and then 440 mg of ketone **41** is
added in drops to 2 ml of THF. After 1 hour at -78°C, 500 mg of
aldehyde **30** in 10 ml of THF is added, and it is stirred for one
more hour. The reaction mixture is then stirred into ice-cold
ammonium chloride solution and extracted with ethyl acetate.
After the organic phase is dried on sodium sulfate, the solvent
is removed and chromatographed on silica gel with ethyl
acetate/hexane, whereby 529 mg of (5Z,7E)-(1S,3R)-1,3-
bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-22-hydroxy-25-(4-
methyl-phenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-
one **54** is obtained as a colorless foam.

529 mg of **54** is dissolved in 20 ml of toluene, mixed with
0.34 ml of acetic anhydride, 0.49 ml of triethylamine as well as
a spatula tip full of dimethylaminopyridine (DMAP), and it is
stirred overnight under nitrogen at room temperature. Then, the
reaction mixture is treated with sodium bicarbonate solution and
extracted with ethyl acetate. After the organic phase is dried

on sodium sulfate and after chromatography on silica gel with
ethyl acetate/hexane, 439 mg of (5Z,7E)-(1S,3R)-22-(acetyloxy)-
1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-
methylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-
one **55** is obtained as a colorless foam, which is dissolved in 20
ml of toluene and is stirred with 3 ml of 1,8-
diazabicyclo[5.4.0]undec-7-ene (DBU) for 30 minutes at 40°C under
nitrogen. The reaction mixture is diluted with ethyl acetate and
acidified with 0.01N hydrochloric acid. It is extracted with
ethyl acetate, dried on sodium sulfate, and the solvent is
removed, whereby 395 mg of (5Z,7E,22E)-(1S,3R)-1,3-
bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-methylphenyl)-
26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-one **56** is
obtained as a colorless oil.

56: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.05 ppm (s, 6H); 0.49
(s, 3H); 0.89 (s, 18H); 0.97 (d, 3H); 1.11 (m, 4H); 2.38 (s, 3H);
4.19 (m, 1H); 4.38 (m, 1H); 4.86 (s, 1H); 5.18 (s, 1H); 5.99 (d,
1H); 6.01 (d, 1H); 6.22 (d, 1H); 6.63 (d, 1H); 7.15 (d, 2H); 7.22
(d, 2H)

395 mg of enone **56** is dissolved in 2 ml of THF and 4 ml of
methanol and treated at 0°C under nitrogen with 217 mg of cerium
trichloride (heptahydrate). Then, 18 mg of sodium borohydride is
added, and it is stirred for 2 more hours at 0°C. Ice water is
now added, extracted with ethyl acetate and dried on sodium
sulfate. The residue is chromatographed on silica gel with ethyl
acetate/hexane, whereby in the elution sequence, 115 mg of
(5Z,7E,24R)-1,3-bis[[dimethyl(1,1-

dimethylethyl)silyl]oxy]-25-(4-methylphenyl)-26,27-cyclo-9,10-
secocholesta-5,7,10(19),20(22)-tetraen-24-ol **57b**, 50 mg of
(5Z,7E,22E)-(1S,3R,24S)-1,3-bis[[dimethyl(1,1-
dimethylethyl)silyl]oxy]-25-(4-methylphenyl)-26,27-cyclo-9,10-
secocholesta-5,7,10(19),22-tetraen-24-ol **58a** and 30 mg of
(5Z,7E,22E)-(1S,3R,24R)-1,3-bis[[dimethyl(1,1-
dimethylethyl)silyl]oxy]-25-(4-methylphenyl)-26,27-cyclo-9,10-
secocholesta-5,7,10(19),22-tetraen-24-ol **58b** accumulate as
colorless foams.

115 mg of **57b** is dissolved in 15 ml of THF and stirred under
nitrogen with 468 mg of tetrabutylammonium fluoride (trihydrate)
overnight at room temperature. Saturated sodium bicarbonate
solution is then added and extracted with ethyl acetate. The
combined organic phases are washed with water, dried on sodium
sulfate and concentrated by evaporation. Chromatography of the
residue on silica gel with ethyl acetate/hexane yields 31 mg of
title compound **59b** as a colorless foam.

^{1}H-NMR (300 MHz, CD$_2$Cl$_2$): δ = 0.41 ppm (s, 3H); 1.56 (s,
3H); 2.30 (s, 3H); 3.17 (m, 1H); 4.18 (m, 1H); 4.38 (m, 1H); 4.96
(s, 1H); 5.22 (t, 1H); 5.28 (s, 1H); 6.01 (d, 1H); 6.34 (d, 1H);
7.08 (d, 2H); 7.22 (d, 2H)

Analogously to **59b**, title compounds **60a** and **60b** are obtained
as colorless foams from **58a** and **58b**.

60a: ^{1}H-NMR (300 MHz, CD$_2$Cl$_2$): δ = 0.52 ppm (s, 3H); 0.99
(d, 3H); 2.28 (s, 3H); 3.67 (m, 1H); 4.18 (m, 1H); 4.38 (m, 1H);

4.96 (s, 1H); 5.28 (dd, 1H); 5.29 (s, 1H); 5.39 (dd, 1H); 6.01

(d, 1H); 6.36 (d, 1H); 7.08 (d, 1H); 7.19 (d, 1H)

   60b: ^{1}H-NMR (300 MHz, CD$_2$Cl$_2$): δ = 0.53 ppm (s, 3H); 0.98

(d, 3H); 3.28 (s, 3H); 3.70 (m, 1H); 4.18 (m, 1H); 4.38 (m, 1H);

4.96 (s, 1H); 5.27 (dd, 1H); 5.29 (s, 1H); 5.37 (dd, 1H); 6.01

(d, 1H); 6.36 (d, 1H); 7.09 (d, 1H); 7.20 (d, 1H)

Example 11

(5Z,7E)-(1S,3R,24R)-25-[4-(1-Methylethyl)phenyl]-26,27-cyclo-

9,10-secocholesta-5,7,10(19),20(22)-tetraene-1,3,24-triol **66b**,

(5Z,7E,22E)-(1S,3R,24S)-25-[4-(1-methylethyl)-phenyl]-26,27-

cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **67a**

and (5Z,7E,22E)-(1S,3R,24R)-25-[4-(1-methylethyl)phenyl]-26,27-

cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **67b**

   1.11 ml of n-butyllithium solution (1.6 M in hexane) is

added in drops at 0°C to 0.36 ml of diisopropylamine in 10 ml of

THF under nitrogen. It is stirred for 20 minutes at this

temperature, cooled to -78°C, and then 560 mg of ketone **47** is

added in drops to 2 ml of THF. After 1 hour at -78°C, 500 mg of

aldehyde **30** is added to 10 ml of THF, and it is stirred for 1

more hour. The reaction mixture is then treated with ammonium

chloride solution and extracted with ethyl acetate. After the

organic phase is dried on sodium sulfate, the solvent is removed

and chromatographed on silica gel with ethyl acetate/hexane,

whereby 497 mg of (5Z,7E)-(1S,3R)-1,3-bis[[dimethyl(1,1-

dimethylethyl)silyl]oxy]-22-hydroxy-25-[4-(1-methyl-

ethyl)phenyl]-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-one **61** is obtained as a colorless foam.

490 mg of **61** is dissolved in 20 ml of toluene, mixed with 0.30 ml of acetic anhydride, 0.44 ml of triethylamine as well as a spatula tip full of dimethylaminopyridine (DMAP), and it is stirred overnight under nitrogen at room temperature. Then, the reaction mixture is treated with sodium bicarbonate solution and extracted with ethyl acetate. After the organic phase is dried on sodium sulfate and after chromatography on silica gel with ethyl acetate/hexane, 379 mg of (5Z,7E)-(1S,3R)-22-(acetyloxy)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-[4-(1-methylethyl)phenyl]-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-one **62** is obtained as a colorless foam, which is dissolved in 20 ml of toluene and is stirred with 3 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 30 minutes at 40°C under nitrogen. The reaction mixture is diluted with ethyl acetate and acidified with 0.01N hydrochloric acid. It is extracted with ethyl acetate, dried on sodium sulfate and the solvent is removed, whereby 355 mg of (5Z,7E,22E)-(1S,3R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-[4-(1-methylethyl)phenyl]-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-one **63** is obtained as a colorless oil.

63: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.06 ppm (s, 6H); 0.48 (s, 3H); 0.90 (s, 18H); 0.98 (d, 3H); 1.29 (d, 6H); 2.92 (hept, 1H); 4.18 (m, 1H); 4.37 (m, 1H); 4.85 (s, 1H); 5.18 (s, 1H); 5.95 (d, 1H); 6.00 (d, 1H); 6.22 (d, 1H); 6.60 (d, 1H); 7.20 (d, 2H); 7.23 (d, 2H).

350 mg of enone **63** is dissolved in 2 ml of THF and 4 ml of methanol and treated at 0°C under nitrogen with 190 mg of cerium trichloride heptahydrate. Then, 16 mg of sodium borohydride is added, and it is stirred for 2 more hours at 0°C. Ice water is now added, extracted with ethyl acetate and dried on sodium sulfate. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby in the elution sequence, 27 mg of (5Z,7E)-(1S,3R,24R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-[4-(1-methylethyl)phenyl]-26,27-cyclo-9,10-secocholesta-5,7,10(19),20(22)-tetraen-24-ol **64b**, 40 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-[4-(1-methylethyl)phenyl]-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **65a** and 48 mg of (5Z,7E,22E)-(1S,3R,24R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-[4-(1-methylethyl)phenyl]-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **65b** accumulate as colorless foams.

27 mg of **64b** is dissolved in 5 ml of THF and stirred under nitrogen with 112 mg of tetrabutylammonium fluoride (trihydrate) overnight at room temperature. Saturated sodium bicarbonate solution is then added and extracted with ethyl acetate. The combined organic phases are washed with water, dried on sodium sulfate and concentrated by evaporation. Chromatography of the residue on silica gel with ethyl acetate/hexane yields 12 mg of title compound **66b** as a colorless foam.

^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 0.45 ppm (s, 3H); 1.23 (d, 6H); 1.56 (s, 3H); 2.86 (hept, 1H); 3.18 (m, 1H); 4.17 (m, 1H);

4.37 (m, 1H); 4.96 (s, 1H); 5.18 (s, 1H); 5.25 (t, 1H); 6.00 (d, 1H); 6.36 (d, 1H); 7.14 (d, 2H); 7.27 (d, 2H)

Analogously to **66b**, title compounds **67a** and **67b** are obtained as colorless foams from **65a** and **65b**.

67a: ^{1}H-NMR (300 MHz, CD$_2$Cl$_2$): δ = 0.52 ppm (s, 3H); 0.98 (d, 3H); 1.20 (d, 6H); 2.86 (hept, 1H); 3.71 (m, 1H); 4.17 (m, 1H); 4.37 (m, 1H); 4.95 (s, 1H); 5.28 (s, 1H); 5.30 (dd, 1H); 5.39 (dd, 1H); 5.99 (d, 1H); 6.34 (d, 1H); 7.10 (d, 1H); 7.22 (d, 1H)

67b: ^{1}H-NMR (300 MHz, CD$_2$Cl$_2$): δ = 0.53 ppm (s, 3H); 0.99 (d, 3H), 1.21 (d, 6H); 2.86 (hept, 1H); 367 (m, 1H); 4.17 (m, 1H); 4.37 (m, 1H); 4.96 (s, 1H); 5.28 (s, 1H); 5.29 (dd, 1H); 5.38 (dd, 1H); 6.01 (d, 1H); 6.37 (d, 1H); 7.13 (d, 1H); 7.25 (d, 1H)

Example 12

(5Z,7E)-(1S,3R,24R)-25-(4-Butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),20(22)-tetraene-1,3,24-triol **73b**, (5Z,7E,22E)-(1S,3R,24S)-25-(4-butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **74a**, and (5Z,7E,22E)-(1S,3R,24R)-25-(4-butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **74b**

1.28 ml of n-butyllithium solution (1.6 M in hexane) is added in drops at 0°C to 0.42 ml of diisopropylamine in 10 ml of THF under nitrogen. It is stirred for 20 minutes at this temperature, cooled to -78°C and then 692 mg of ketone **53** is added in drops to 4 ml of THF. After 1 hour at -78°C, 484 mg of

aldehyde **30** is added to 10 ml of THF, and it is stirred for 1 more hour. The reaction mixture is then treated with ammonium chloride solution and extracted with ethyl acetate. After the organic phase is dried on sodium sulfate, the solvent is removed and chromatographed on silica gel with ethyl acetate/hexane, whereby 456 mg of (5Z,7E)-(1S,3R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-butylphenyl)-22-hydroxy-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-one **68** is obtained as a colorless foam.

450 mg of **68** is dissolved in 18 ml of toluene, mixed with 0.27 ml of acetic anhydride, 0.40 ml of triethylamine and a spatula tip full of dimethylaminopyridine (DMAP), and it is stirred overnight under nitrogen at room temperature. Then, the reaction mixture is treated with sodium bicarbonate solution and extracted with ethyl acetate. After the organic phase is dried on sodium sulfate and after chromatography on silica gel with ethyl acetate/hexane, 399 mg of (5Z,7E)-(1S,3R)-22-(acetyloxy)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19)-trien-24-one **69** is obtained as a colorless foam, which is dissolved in 18 ml of toluene and is stirred with 2.7 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 30 minutes at 40°C under nitrogen. The reaction mixture is diluted with ethyl acetate and acidified with 0.01N hydrochloric acid. It is extracted with ethyl acetate, dried on sodium sulfate, and the solvent is removed, whereby 357 mg of (5Z,7E,22E)-(1S,3R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-butylphenyl)-

26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-one **70** is obtained as a colorless oil.

70: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.08 ppm (s, 6H); 0.48 (s, 3H); 0.89 (s, 18H); 0.93 (t, 3H); 0.95 (d, 3H); 2.62 (t, 2H); 4.19 (m, 1H); 4.38 (m, 1H); 4.86 (s, 1H); 5.18 (s, 1H); 5.97 (d, 1H); 6.00 (d, 1H); 6.22 (d, 1H); 6.63 (d, 1H); 7.16 (d, 2H); 7.22 (d, 2H)

350 mg of enone **70** is dissolved in 2 ml of THF and 4 ml of methanol and treated at 0°C under nitrogen with 186 mg of cerium trichloride heptahydrate. Then, 16 mg of sodium borohydride is added, and it is stirred for 2 more hours at 0°C. Ice water is now added, extracted with ethyl acetate, and dried on sodium sulfate. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby in the elution sequence, 24 mg of (5Z,7E)-(1S,3R,24R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),20(22)-tetraen-24-ol **71b**, 40 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **72a** and 51 mg of (5Z,7E,22E)-(1S,3R,24R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-butylphenyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **72b** accumulate as colorless foams.

24 mg of **71b** is dissolved in 5 ml of THF, and stirred under nitrogen with 97 mg of tetrabutylammonium fluoride (trihydrate) overnight at room temperature. Saturated sodium bicarbonate

solution is then added and extracted with ethyl acetate. The combined organic phases are washed with water, dried on sodium sulfate and concentrated by evaporation. Chromatography of the residue on silica gel with ethyl acetate/hexane yields 13 mg of title compound **73b** as a colorless foam.

^{1}H-NMR (300 MHz, CD$_2$Cl$_2$): δ = 0.42 ppm (s, 3H); 0.91 (t, 3H); 1.68 (s, 3H); 2.58 (t, 2H); 3.18 (m, 1H); 4.17 (m, 1H); 4.38 (m, 1H); 4.98 (s, 1H); 5.25 (t, 1H); 5.30 (s, 1H); 6.02 (d, 1H); 6.36 (d, 1H); 7.09 (d, 2H); 7.27 (d, 2H)

Analogously to **73b**, title compounds **74a** and **74b** are obtained as colorless foams from **72a** and **72b**.

74a: ^{1}H-NMR (300 MHz, CD$_2$Cl$_2$): δ = 0.55 ppm (s, 3H); 0.92 (t, 3H); 0.98 (d, 3H); 2.58 (t, 2H); 3.71 (m, 1H); 4.16 (m, 1H); 4.37 (m, 1H); 4.97 (s, 1H); 5.29 (s, 1H); 5.31 (dd, 1H); 5.39 (dd, 1H); 6.00 (d, 1H); 6.36 (d, 1H); 7.08 (d, 1H); 7.23 (d, 1H)

74b: ^{1}H-NMR (300 MHz, CD$_2$Cl$_2$): δ = 0.56 ppm (s, 3H); 0.93 (t, 3H); 0.98 (d, 3H); 2.58 (t, 2H); 3.68 (m, 1H); 4.17 (m, 1H); 4.38 (m, 1H); 4.98 (s, 1H); 5.28 (dd, 1H); 5.29 (s, 1H); 5.38 (dd, 1H); 6.01 (d, 1H); 6.37 (d, 1H); 7.08 (d, 1H); 7.22 (d, 1H)

Synthesis of the Starting Materials in the 4-Alkyloxazole Series
2-(1-Bromocyclopropyl)-4-methyloxazole **77**

7.45 g of N,N'-dicyclohexylcarbodiimide is added at 0°C under nitrogen to a solution of 5.0 g of 1-bromocyclopropanecarboxylic acid **4** and 4.18 g of N-hydroxysuccinimide in 87 ml of methylene chloride, and it is stirred for 1.5 more hours. Then, 9.40 g of 2-

aminopropionaldehyde dimethylacetal is added, and it is stirred for 2 hours at room temperature. After dilution with methylene chloride, it is filtered, concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane. 6.18 g of 1-bromo-N-[(2,2-dimethoxy-1-methyl)ethyl]-cyclopropane-1-carboxamide **75** is obtained as a colorless cloudy oil, which is taken up in 247 ml of acetonitrile and is stirred with 12.4 ml of 2N hydrochloric acid for 7 hours at room temperature. After sodium chloride solution is added, it is extracted with ethyl acetate, dried on sodium sulfate, and the solvent is removed. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 3.83 g of 1-bromo-N-[(1-formyl)ethyl]cyclopropyl-1-carboxamide **76** accumulates.

3.43 g of amide **76**, 5.54 g of hexachloroethane and 7.62 ml of triethylamine are dissolved in 47 ml of acetonitrile and cooled to -25°C. 6.14 g of triphenylphosphine is added, and it is stirred for 4.5 more hours at room temperature. It is now filtered, concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 2.06 g of title compound **77** is obtained as a yellow oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.50 ppm (m, 2H); 1.65 (m, 2H); 2.13 (s, 3H); 7.32 (s, 1H)

2-(1-Bromocyclopropyl)-4-ethyloxazole **80**

7.45 g of N,N'-dicyclohexylcarbodiimide is added at 0°C under nitrogen to a solution of 5.0 g of 1-bromocyclopropanecarboxylic acid **4** and 4.18 g of N-

hydroxysuccinimide in 87 ml of methylene chloride, and it is stirred for 1.5 more hours. Then, 7.46 ml of 2-amino-1-butanol is added, and it is stirred for 2 hours at room temperature. After dilution with methylene chloride, it is filtered, concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane. 5.44 g of 1-bromo-N-[(1-hydroxymethyl)propyl]-cyclopropane-1-carboxamide **78** is obtained as a yellowish oil.

2.23 ml of oxalyl chloride in 102 ml of methylene chloride is mixed drop by drop at -78°C under nitrogen with 3.6 ml of dimethylsulfoxide in 41 ml of methylene chloride. Then, 5.43 g of amide alcohol **78** in 41 ml of methylene chloride and, after 15 minutes, 14.3 ml of triethylamine are added in drops at -78°C. After another 30 minutes, sodium chloride solution is added, extracted with methylene chloride, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 3.4 g of 1-bromo-N-[(1-formyl)propyl]-cyclopropane-1-carboxamide **79** is obtained as a yellow oil, which is converted into title compound **80** analogously to the reaction of amide **76**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.19 ppm (t, 3H); 1.50 (m, 2H); 1.62 (m, 2H); 2.50 (q, 2H); 7.29 (s, 1H)

2-(1-Bromocyclopropyl)-4-propyloxazole **81**

Analogously to the synthesis of oxazole **80**, title compound **81** is obtained with use of 2-aminopentanol.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.92 ppm (t, 3H); 1.50 (m, 2H); 1.62 (m, 4H); 2.45 (t, 2H); 7.30 (s, 1H)

Example 13

(5Z,7E,22E)-(1S,3R,24S)-25-(4-Methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **83a** and (5Z,7E,22E)-(1S,3R,24R)-25-(4-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **83b**

2.75 ml of **tert**-butyllithium (1.7 M in pentane) is introduced at -20°C under nitrogen into 8 ml of diethyl ether, cooled to -78°C, and 505 mg of 2-(1-bromocyclopropyl)-4-methyloxazole **77** is added in drops to 1.15 ml of diethyl ether. After 5 minutes, aldehyde **3** is added in drops to 3 ml of diethyl ether, it is stirred for 10 minutes at -78°C and then allowed to reach 0°C within 1.5 hours. Then, ammonium chloride solution is added, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby in the elution sequence, 180 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **82a** and 180 mg of (5Z,7E,22E)-(1S,3R,24R)-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(4-methyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **82b** is obtained as colorless oils. 180 mg of disilyl ether **82a** is dissolved in 7.3 ml of THF and stirred with 384 mg of tetrabutylammonium fluoride (trihydrate) overnight at room temperature under nitrogen. A

mixture of sodium chloride and sodium bicarbonate solution is then added, extracted with ethyl acetate, the organic phase is washed with sodium chloride solution, dried on sodium sulfate, and the solvent is removed. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 63 mg of title compound **83a** is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 1.00 (d, 3H); 1.05 (m, 4H); 2.11 (s, 3H); 4.10 (m, 2H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.42 (dd, 1H); 5.58 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 7.18 (s, 1H)

Title compound **83b** is analogously obtained as a colorless foam from disilyl ether **82b**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 0.98 (d, 3H); 1.05 (m, 4H), 2.08 (s, 3H); 4.08 (m, 1H); 4.21 (m, 1H); 4.40 (m, 1H); 4.48 (brs, 1H); 5.30 (brs, 1H); 5.40 (dd, 1H); 5.51 (dd, 1H); 5.98 (d, 1H); 6.35 (d, 1H); 7.18 (s, 1H)

Example 14

(5Z,7E,22E)-(1S,3R,24R)-25-(4-Ethyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **84b**

Analogously to Example 13, title compound **84b** is obtained as a colorless foam from aldehyde **3** and oxazole **80**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 0.98 (d, 3H); 1.08 (t, 3H); 2.48 (q, 2H); 4.09 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 4.47 (brs, 1H); 5.30 (brs, 1H); 5.40 (dd, 1H); 5.52 (dd, 1H); 6.00 (d, 1H); 6.36 (d, 1H); 7.15 (s, 1H)

Example 15

(5Z,7E,22E)-(1S,3R,24R)-25-(4-Propyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **85b**

Analogously to Example 13, title compound **85b** is obtained as a colorless foam from aldehyde **3** and oxazole **81**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.50 ppm (s, 3H); 0.91 (t, 3H); 0.98 (d, 3H); 1.20 (m, 4H); 2.40 (t, 2H); 4.08 (d, 1H); 4.20 (m, 1H); 4.40 (m, 1H); 4.45 (brs, 1H); 5.28 (brs, 1H); 5.38 (dd, 1H); 5.50 (dd, 1H); 5.95 (d, 1H); 6.45 (d, 1H); 7.15 (s, 1H)

Example 16

(5Z,7E,22E)-(1S,3R,24R)-25-(5-Butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **88b**

1-Bromo-N-(2-oxohexyl)-cyclopropane-1-carbamide **86** is produced analogously to amide **6**, and converted into 2-(1-bromocyclopropyl)-5-butyloxazole **87** as described for compound **8**.

87: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.92 ppm (t, 3H); 1.40 (m, 2H); 1.50 (m, 2H); 1.60 (m, 4H); 2.60 (t, 2H); 6.65 (s, 1H)

Analogously to Example 1, title compound **88b** is obtained as a colorless foam from aldehyde **3** and oxazole **87**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.57 ppm (s, 3H); 0.90 (t, 3H); 0.97 (m, 2H); 1.05 (d, 3H); 1.15 (m, 2H); 2.58 (m, 3H); 4.12 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.42 (dd, 1H); 5.53 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.58 (s, 1H)

Starting Materials in the 5-Alkyl-Thiazole Series

2-(1-Bromocyclopropyl)-5-butylthiazole 89

500 mg of amide **86** and 212 mg of phosphorus pentasulfide are heated in 2 ml of dioxane for 25 minutes to 100°C and, after cooling, poured into dilute sodium hydroxide solution. After extraction with ethyl acetate and drying on sodium sulfate, it is concentrated by evaporation, and the oily residue is chromatographed on silica gel with ethyl acetate/hexane. 240 mg of title compound **89** is obtained as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.92 ppm (t, 3H); 1.48 (m, 2H); 1.65 (m, 6H); 2.75 (t, 2H); 7.32 (s, 1H)

2-(1-Bromocyclopropyl)-5-ethylthiazole 90

Analogously to the production of thiazole **89**, title compound **90** is obtained as a colorless oil from amide **9**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.28 ppm (t, 3H); 1.58 (m, 2H); 1.70 (m, 2H); 2.80 (q, 2H); 7.32 (s, 1H)

Example 17

(5Z,7E,22E)-(1S,3R,24S)-25-(5-Butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol 92a and **(5Z,7E,22E)-(1S,3R,24R)-25-(5-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol 92b**

5.9 ml of **tert-butyllithium** (1.7 M in pentane) is added at -78°C under nitrogen to 16 ml of Trapp mixture (THF/diethyl ether/pentane 4:1:1). At -116°C, 1.3 g of thiazole **89** is added in drops to 2.4 ml of Trapp mixture. After 1 hour, 1.0 g of

aldehyde **3** is added to 6.4 ml of Trapp mixture, and it is stirred for 1 hour at -116°C and for 1 hour at -78°C. It is then quenched with ammonium chloride solution, extracted with diethyl ether and dried on sodium sulfate. After concentration by evaporation, the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby in the elution sequence, 470 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(5-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **91a** and 440 mg of (5Z,7E,22E)-(1S,3R,24R)-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(5-butylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **91b** accumulate as yellow oils.

460 mg of disilyl ether **91a** is dissolved in 17 ml of THF and treated under nitrogen with 900 mg of tetrabutylammonium fluoride (trihydrate). It is stirred overnight and then a mixture of sodium chloride and sodium bicarbonate solution is added. Then, it is extracted with ethyl acetate, the organic phase is washed with sodium chloride solution, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel, whereby 139 mg of title compound **92a** is obtained as a colorless foam.

92a: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 0.92 (t, 3H); 0.98 (d, 3H); 1.08 (m, 4H); 2.75 (t, 2H); 4.00 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.40 (dd, 1H); 5.55 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 7.25 (s, 1H)

Title compound **92b** is obtained analogously as a colorless foam from disilyl ether **91b**.

92b: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 0.92 (t, 3H); 0.98 (d, 3H); 1.08 (m, 4H); 2.75 (t, 2H); 4.00 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.40 (dd, 1H); 5.55 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 7.25 (s, 1H)

Example 18

(5Z,7E,22E)-(1S,3R,24R)-25-(5-Ethylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **93b**

Analogously to Example 17, starting from aldehyde **3**, the title compound is obtained as a colorless foam with thiazole **90**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 0.98 (d, 3H); 1.08 (m, 4H); 1.28 (t, 3H); 2.80 (q, 2H); 4.01 (d, 1H); 4.23 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.40 (dd, 1H); 5.52 (dd, 1H); 6.00 (d, 1H); 6.37 (d, 1H); 7.28 (s, 1H)

Example 19

(5Z,7E,22E)-(1S,3R,24S)-25-(3-Butyl-1,2,4-oxadiazol-5-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **95a**

28 mg of sodium is dissolved in 0.8 ml of methanol, and 200 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-24-hydroxy-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-25-carboxylic acid methyl ester **94a** (for production, see DE 42 34 382) is added under nitrogen to 0.8 ml of methanol and 55 mg of valerylamidoxime [K. P. Flora et al. **Cancer Res.** 1291 (1978)] and heated to boiling

for 9.25 hours. The reaction mixture is added to sodium chloride solution, extracted with ethyl acetate, and the organic phase is washed with sodium chloride solution. After drying with sodium sulfate and concentration by evaporation, the oily residue is purified chromatographically on silica gel with ethyl acetate/hexane, whereby 40 mg of title compound **95a** is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 0.95 (t, 3H); 1.02 (d, 3H); 1.20 (m, 4H); 2.68 (t, 2H); 4.23 (m, 2H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.42 (dd, 1H); 5.62 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H)

Example 20

(5Z,7E,22E)-(1S,3R,24R)-25-(3-Butyl-1,2,4-oxadiazol-5-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **95b**

Analogously to Example 20, starting from (5Z,7E,22E)-(1S,3R,24R)-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-24-hydroxy-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-25-carboxylic acid methyl ester **94b** (for production, see DE 42 34 382), title compound **95b** is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 0.92 (t, 3H); 1.03 (d, 3H); 1.20 (m, 4H); 2.70 (t, 2H); 3.55 (brd, 1H); 4.23 (m, 2H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.43 (dd, 1H); 5.58 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H)

Example 21

(5Z,7E,22E)-(1S,3R,24R)-25-(3-Ethyl-1,2,4-oxadiazol-5-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **96b**

Analogously to Example 20, starting from (5Z,7E,22E)-(1S,3R,24R)-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-24-hydroxy-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-25-carboxylic acid methyl ester **94b** (for production, see DE 42 34 382), title compound **96b** is obtained as a colorless foam with propionamidoxime [K. P. Flora et al. **Cancer Res.** 1291 (1978)].

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.52 ppm (s, 3H); 1.02 (d, 3H); 1.20 (m, 4H); 1.32 (t, 3H); 2.75 (q, 2H); 4.23 (m, 2H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.43 (dd, 1H); 5.58 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H)

Starting Materials for the 25-Pyridyl Series

2-(1-Bromocyclopropyl)-pyridine **100**

10.0 g of 1-bromocyclopropanecarboxylic acid **4**, 7.0 g of 2-pyridine thiol and 13.8 g of N,N'-dicyclohexylcarbodiimide are dissolved in 150 ml of ethyl acetate and stirred for 2 hours under nitrogen at room temperature. After sodium chloride solution is added, it is extracted with ethyl acetate, the organic phase is washed with saturated sodium chloride solution, dried on sodium sulfate and concentrated by evaporation. The oily residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 8.25 g of 1-bromo-S-(2-pyridyl)-cyclopropanethioate **97** is obtained as a yellow oil. 10.11 g of thioester **97** in 26 ml of THF is mixed drop by drop at 0°C with 3-

(1,3-dioxolan-2-yl)-propylmagnesium bromide **98** [D. Wenkert et al.
J. Org. Chem. 50, 4114 (1985)]. After 3 hours at room
temperature, the suspension in stirred into ammonium chloride
solution and extracted with ethyl acetate. It is dried on sodium
sulfate, concentrated by evaporation, and the residue is
chromatographed on silica gel with ethyl acetate/hexane, whereby
7.92 g of 1-(1-bromocyclopropyl)-4-(1-dioxolan-2-yl)-butan-1-one
99 is obtained as a colorless oil. 6.68 g of ketone **99** in 76 ml
of acetic acid is heated to boiling with 5.08 g of hydroxylamine
hydrochloride for 1 hour under nitrogen. After the acetic acid
is evaporated, the oily residue is mixed with ice and made basic
with about 20% sodium hydroxide solution. Then, it is diluted
with sodium chloride solution and extracted with ethyl acetate.
The organic phase is dried on sodium sulfate and concentrated by
evaporation. The residue is chromatographed on silica gel with
ethyl acetate/hexane, whereby 2.73 g of title compound **100** is
obtained as a light yellow oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.55 ppm (m, 2H); 1.68 (m,
2H); 7.10 (m, 1H); 7.65 (m, 1H); 7.75 (m, 1H); 8.48 (m, 1H)

2-(1-Bromocyclopropyl)-6-methylpyridine **103**

Starting from 1-(1-bromocyclopropyl)-5,5-ethylenedioxyhexan-
1-one **102**, which is obtained by reaction of thioester **97** with
Grignard reagent **101** [S. Borrelly, L. A. Paquette **J. Am. Chem.
Soc. 118**, 727 (1996), T. E. Bellas et al. **Tetrahedron 25**, 5149
(1969)], title compound **103** is produced analogously to **99**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.50 ppm (m, 2H); 1.65 (m, 2H); 2.50 (s, 3H); 6.98 (m, 1H); 7.52 (m, 2H)

Example 22

(5Z,7E,22E)-(1S,3R,24S)- 25-(2-Pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **105a** and

(5Z,7E,22E)-(1S,3R,24R)-25-(2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **105b**

At -20°C, 8.5 ml of **tert**-butyllithium (1.7 M in pentane) is added under nitrogen to 24 ml of diethyl ether. At -78°C, 1.34 g of **100** is added in drops to 3.2 ml of diethyl ether, and it is stirred for 30 minutes at -78°C. Then, 1.34 g of aldehyde **3** is added in drops to 8.3 ml of diethyl ether, stirred for another 30 minutes at -78°C and then allowed to reach 0°C within 90 minutes. Then, it is quenched with ammonium chloride solution, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby in the elution sequence, 120 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-25-(2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **104a** and 100 mg of (5Z,7E,22E)-(1S,3R,24R)-1,3-bis-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-25-(2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **104b** are obtained as colorless foams in each case.

120 mg of disilyl compound **104a** is dissolved in 4.8 ml of THF and stirred with 257 mg of tetrabutylammonium fluoride (trihydrate) under nitrogen overnight at room temperature. The

reaction mixture is then poured into a mixture of sodium chloride and sodium bicarbonate solution, extracted with ethyl acetate, the organic phase is washed with sodium chloride solution, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 19 mg of title compound **105a** accumulates as a colorless foam.

105a: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.48 ppm (s, 3H); 0.88 (m, 4H); 0.95 (d, 3H); 3.88 (d, 1H); 4.23 (m, 2H); 4.43 (m, 1H); 4.98 (brs, 1H); 5.32 (brs, 1H); 5.38 (dd, 1H); 5.50 (dd, 1H); 5.98 (d, 1H); 6.38 (d, 1H); 6.98 (d, 1H); 7.12 (brt, 1H); 7.60 (brt, 1H); 8.45 (d, 1H)

Disilyl ether **104b** is treated analogously with tetrabutylammonium fluoride (trihydrate), whereby title compound **105b** is obtained as a colorless foam.

105b: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.50 ppm (s, 3H); 0.88 (m, 4H); 0.95 (d, 3H); 3.88 (d, 1H); 4.23 (m, 2H); 4.43 (m, 1H); 4.98 (brs, 1H); 5.32 (brs, 1H); 5.40 (m, 2H); 6.00 (d, 1H); 6.38 (d, 1H); 6.98 (d, 1H); 7.12 (brt, 1H); 7.60 (brt, 1H); 8.45 (d, 1H)

Example 23

(5Z,7E,22E)-(1S,3R,24R)-25-(6-Methyl-2-pyridyl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **106b**

Analogously to Example 22, starting from aldehyde **3**, title compound **106b** is obtained as a colorless foam with pyridine derivative **103**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.50 ppm (s, 3H); 0.85 (m, 4H); 0.95 (d, 3H); 2.51 (s, 3H); 3.80 (d, 1H); 4.23 (m, 2H); 4.43 (m, 1H); 4.98 (brs, 1H); 5.32 (brs, 1H); 5.40 (m, 2H); 5.48 (d, 1H); 6.38 (d, 1H); 6.45 (d, 1H); 6.70 (d, 1H); 7.48 (t, 1H)

Starting Materials in the 25-Oxazoline Series

2-(1-Bromocyclopropyl)-5,5-dimethyl-2-oxazoline **109**

47 g of carboxylic acid **4** is mixed under nitrogen with 78 ml of thionyl chloride, and it is stirred overnight at room temperature. Then, excess thionyl chloride is distilled off, and the residue is fractionated in an oil pump vacuum, whereby 44.74 g of 1-bromocyclopropane-carboxylic acid chloride **107** accumulates as a colorless oil (boiling point 35-37°C, 0.05 mm).

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.69 ppm (m, 2H); 2.09 (m, 2H)

1.69 g of 2-amino-2-methyl-1-propanol is introduced into 85 ml of methylene chloride under nitrogen at room temperature, and 2.38 g of sodium carbonate is added to 38 ml of water and then 3.6 g of acid chloride **107**. It is stirred overnight at room temperature and then treated with methanolic 2N sodium hydroxide solution. The organic phase is separated, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 3.83 g of 1-bromocyclopropanecarboxylic acid-1,1-dimethyl-2-hydroxy-ethylamide **108** is obtained as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.32 ppm (m, 2H); 1.33 (s, 6H); 1.68 (m, 2H); 3.61 (d, 2H); 4.25 (t, 1H); 6.87 (brs, 1H)

800 mg of amide 107 is dissolved in 8 ml of toluene, and 3 ml of phosphorus oxychloride is added in drops at room temperature under nitrogen. After 30 minutes, it is concentrated by evaporation, the residue is taken up in methylene chloride and stirred vigorously with 10 ml of sodium carbonate solution (10%) for 30 minutes. The phases are separated, the organic phase is dried on sodium sulfate, filtered and concentrated by evaporation, whereby 750 mg of title compound 109 accumulates as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.29 ppm (s, 6H), 1.38 (m, 2H); 1.58 (m, 2H); 4.01 (s, 2H)

(5R)-2-(1-Bromocyclopropyl)-5-phenyl-2-oxazoline 111

739 mg of D-(-)-α-phenylglycinol is dissolved in 27 ml of methylene chloride, and 678 mg of sodium carbonate is added to 11 ml of water and 1.09 g of acid chloride 107 at room temperature. It is stirred overnight and then mixed with methanolic sodium hydroxide solution, the organic phase is separated, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 1.09 g of (1R)-1-bromocyclopropanecarboxylic acid-2-hydroxy-1-phenylethylamide 110 is isolated as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.35 ppm (s, 2H); 1.70 (m, 2H); 2.30 (t, 1H); 3.90 (t, 2H); 5.03 (m, 1H); 7.37 (m, 5H); 7.52 (brs, 1H)

Analogously to 107, amide 110 is converted into title compound 111.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.46 ppm (m, 2H); 1.69 (m, 2H); 4.21 (t, 1H); 4.72 (dd, 1H); 5.23 (dd, 1H); 7.30 (m, 5H)

2-(1-Bromocyclopropyl)-5-methyl-2-oxazoline 113

Analogously to the production of amide 110, 2.18 g of acid chloride 107 is reacted with 780 mg of DL-2-amino-1-propanol, whereby 1.7 g of 1-bromocyclopropanecarboxylic acid-2-hydroxy-1-methylethylamide 112 is obtained as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.22 ppm (d, 3H); 1.32 (m, 2H); 1.70 (m, 2H); 2.60 (t, 1H); 3.58 (m, 1H); 3.69 (m, 1H); 4.03 (m, 1H); 6.92 (brs, 1H)

Analogously to 107, amide 112 is converted into title compound 113.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 1.28 ppm (d, 3H); 1.40 (m, 2H); 1.59 (m, 2H); 3.87 (t, 2H); 4.22 (m, 1H); 4.44 (dd, 1H)

5(R)-2-(1-Bromocyclopropyl)-5-ethyl-2-oxazoline 115

Analogously to the production of amide 110, 2.18 g of acid chloride 107 is reacted with 962 mg of (-)-2-amino-1-butanol, whereby 2.3 g of (1R)-1-bromocyclopropanecarboxylic acid-2-hydroxy-1-ethylethylamide 114 is obtained as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.98 ppm (t, 3H); 1.32 (m, 2H); 1.70 (m, 2H); 2.60 (t, 1H); 3.58 (m, 1H); 3.69 (m, 1H); 4.03 (m, 1H); 6.92 (brs, 1H)

Analogously to 107, amide 114 is converted into title compound 115.

^{1}H-NMR (300 MHz, CDCl$_{3}$): δ = 0.92 ppm (t, 3H); 1.38 (m, 2H); 1.58 (m, 2H); 1.70 (m, 2H); 3.98 (t, 1H); 4.38 (dd, 1H); 6.90 (brs, 1H)

25-Oxazoline Series

Example 24

(5Z,7E,22E)-(1S,3R,24S)-25-(5,5-Dimethyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **117a** and (5Z,7E,22E)-(1S,3R,24R)-25-(5,5-dimethyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **117b**

2.16 ml of **tert-butyllithium** is introduced under nitrogen into 6 ml of diethyl ether, and it is cooled to -78°C. 430 mg of oxazoline **109** is added in drops to 1 ml of diethyl ether, and it is stirred for 5 more minutes. Then, 400 mg of aldehyde **3** is added to 1 ml of diethyl ether. It is allowed to reach 0°C within 1.5 hours, and it is hydrolyzed with ammonium chloride solution. After extraction with ethyl acetate and drying on sodium sulfate, it is concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 90 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(5,5-dimethyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **116a** and 50 mg of (5Z,7E,22E)-(1S,3R,24R)-1,3-bis-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-25-(5,5-dimethyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-

tetraen-24-ol **116b** are obtained one right after the other as colorless foams.

116a: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.07 ppm (s, 6H); 0.53 (s, 3H); 0.88 (s, 18H); 1.02 (d, 3H); 1.28 (s, 6H): 3.80 (d, 1H); 3.86 (d, 1H); 3.97 (d, 1H); 4.18 (m, 1H); 4.38 (m, 1H); 4.88 (brs, 1H); 4.98 (brs, 1H); 5.19 (brs, 1H); 5.40 (dd, 1H); 5.56 (dd, 1H); 6.01 (d, 1H); 6.23 (d, 1H)

116b: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.07 ppm (s, 6H); 0.53 (s, 3H); 0.88 (s, 18H); 1.03 (d, 3H); 1.28 (s, 3H); 3.80 (d, 1H); 3.86 (d, 1H); 3.94 (d, 1H); 4.18 (m, 1H); 4.38 (m, 1H); 4.88 (brs, 1H); 4.98 (brs, 1H); 5.19 (brs, 1H); 5.40 (dd, 1H); 5.50 (dd, 1H); 6.01 (d, 1H); 6.23 (d, 1H)

90 mg of the disilyl ether is dissolved in 10 ml of THF, 156 mg of tetrabutylammonium fluoride (trihydrate) is added and stirred under nitrogen for 12 hours at room temperature. The reaction mixture is poured into water, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 36 mg of title compound **117a** is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.58 ppm (s, 3H); 0.78 (m, 2H); 0.84 (m, 2H); 1.02 (d, 3H); 1.28 (s, 6H); 3.80 (d, 1H); 3.84 (d, 1H); 3.97 (d, 1H); 4.22 (m, 1H); 4.42 (m, 1H); 5.00 (brs, 1H); 5.33 (brs, 1H); 5.39 (dd, 1H); 5.55 (dd, 1H); 6.01 (d, 1H); 6.38 (d, 1H)

Analogously, disilyl ether **116b** is converted into title compound **117b**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.58 ppm (s, 3H); 0.78 (m, 2H); 0.84 (m, 2H); 1.03 (d, 1H); 1.28 (s, 6H); 3.80 (d, 1H); 3.84 (d, 1H); 3.92 (d, 1H); 4.22 (m, 1H); 4.42 (m, 1H), 5.00 (brs, 1H); 5.32 (brs, 1H); 5.40 (dd, 1H); 5.50 (dd, 1H); 6.01 (d, 1H); 6.38 (d, 1H)

Example 25

(5Z,7E,22E)-[1S,3R,24S,25(R)]-25-(5-Phenyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **119a** and (5Z,7E,22E)-[1S,3R,24R,25(R)]-25-(5-phenyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **119b**

1.84 ml of **tert**-butyllithium is introduced under nitrogen into 5 ml of diethyl ether, and it is cooled to -78°C. 450 mg of oxazoline **111** is added in drops to 1 ml of diethyl ether, and it is stirred for 5 more minutes. Then, 337 mg of aldehyde **3** is added to 1 ml of diethyl ether. It is allowed to reach 0°C within 1.5 hours and hydrolyzed with ammonium chloride solution. After extraction with ethyl acetate and drying on sodium sulfate, it is concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 110 mg of (5Z,7E,22E)-[1S,3R,24S,25(R)]-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(5-phenyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **118a** and 100 mg of (5Z,7E,22E)-[1S,3R,24R,25(R)]-1,3-bis-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-25-(5-phenyl-2-oxazolin-2-yl)-26,27-

cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **118b** are obtained as colorless foams.

110 mg of disilyl ether **118a** is dissolved in 15 ml of THF, 182 mg of tetrabutylammonium fluoride (trihydrate) is added and stirred under nitrogen for 12 hours at room temperature. The reaction mixture is poured into water, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 36 mg of title compound **119a** is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.58 ppm (s, 3H); 0.88 (m, 2H); 0.92 (m, 2H); 1.06 (d, 3H); 4.00 (t, 1H); 4.01 (m, 1H); 4.22 (m, 1H); 4.42 (m, 1H); 4.53 (dd, 1H); 4.82 (brs, 1H) 5.00 (brs, 1H); 5.22 (dd, 1H); 5.33 (brs, 1H), 5.50 (dd, 1H); 5.62 (dd, 1H); 6.01 (d, 1H); 6.38 (d, 1H); 7.30 (m, 5H)

Disilylether **118b** is analogously converted into title compound **119b**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.58 ppm (s, 3H); 0.88 (m, 2H); 0.94 (m, 2H); 1.07 (d, 3H); 3.98 (t, 1H); 4.02 (m, 1H); 4.22 (m, 1H); 4.42 (m, 1H); 4,55 (dd, 1H); 4.90 (brs, 1H): 5.00 (brs, 1H); 5.22 (dd, 1H); 5.32 (brs, 1H), 5.50 (m, 2H); 6.01 (d, 1H); 6.38 (d, 1H); 7.30 (m, 5H)

Example 26

(5Z,7E,22E)-(1S,3R,24S)-25-(5-Methyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **121a** and (5Z,7E,22E)-(1S,3R,24R)-25-(5-methyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **121b**

1.84 ml of **tert**-butyllithium is introduced under nitrogen into 5 ml of diethyl ether, and it is cooled to -78°C. 350 mg of oxazoline **113** is added in drops to 1 ml of diethyl ether, and it is stirred for 5 more minutes. Then, 337 mg of aldehyde **3** is added to 1 ml of diethyl ether. It is allowed to reach 0°C within 1.5 hours and hydrolyzed with ammonium chloride solution. After extraction with ethyl acetate and drying on sodium sulfate, it is concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 110 mg of (5Z,7E,22E)-(1S,3R,24S)-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(5-methyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **120a** and 100 mg of (5Z,7E,22E)-(1S,3R,24R)-1,3-bis-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-25-(5-methyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **120b** are obtained one right after the other as colorless foams. 90 mg of disilyl ether **120a** is dissolved in 12 ml of THF, 156 mg of tetrabutylammonium fluoride (trihydrate) is added, and it is stirred under nitrogen for 12 hours at room temperature. The reaction mixture is poured into water, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl

acetate/hexane, whereby 41 mg of title compound <u>121a</u> is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.56 ppm (s, 3H); 0.87 (m, 4H); 1.04 (d, 3H); 1.28 (d, 3H); 3.69 (t, 1H); 3.99 (d, 1H); 4.22 (m, 3H); 4.42 (m, 1H); 4.53 (dd, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.39 (dd, 1H); 5.54 (dd, 1H); 6.01 (d, 1H); 6.38 (d, 1H)

Analogously, disilyl ether <u>120b</u> is converted into title compound <u>121b</u>.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.56 ppm (s, 3H); 0.87 (m, 4H); 1.03 (d, 3H); 1.26 (d, 3H); 3.67 (t, 1H); 3.95 (d, 1H); 4.22 (m, 3H); 4.42 (m, 1H); 4.53 (dd, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.45 (m, 2H); 6.01 (d, 1H); 6.38 (d, 1H)

Example 27

(5Z,7E,22E)-[1S,3R,24S,25(R)]-25-(5-Ethyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol <u>123a</u> and (5Z,7E,22E)-[1S,3R,24R,25(R)]-25-(5-ethyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol <u>123b</u>

2.17 ml of **tert**-butyllithium is introduced under nitrogen into 6 ml of diethyl ether, and it is cooled to -78°C. 436 mg of oxazoline <u>113</u> is added in drops to 1 ml of diethyl ether, and it is stirred for 5 more minutes. Then, 400 mg of aldehyde <u>3</u> is added to 1 ml of diethyl ether. It is allowed to reach 0°C within 1.5 hours, and it is hydrolyzed with ammonium chloride solution. After extraction with ethyl acetate and drying on

sodium sulfate, it is concentrated by evaporation, and the residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 70 mg of (5Z,7E,22E)-[1S,3R,24S,25(R)]-1,3-bis-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-25-(5-ethyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **122a** and 40 mg of (5Z,7E,22E)-[1S,3R,24R,25(R)]-1,3-bis-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-25-(5-ethyl-2-oxazolin-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraen-24-ol **122b** are obtained one right after the other as colorless foams.

70 mg of disilyl ether **122a** is dissolved in 10 ml of THF, 122 mg of tetrabutylammonium fluoride (trihydrate) is added, and it is stirred under nitrogen for 12 hours at room temperature. The reaction mixture is poured into water, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 36 mg of title compound **123a** is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.57 ppm (s, 3H); 0.79 (m, 2H); 0.85 (m, 2H); 0.96 (t, 3H); 1.03 (d, 3H); 3.78 (t, 1H); 3.99 (d, 1H); 4.13 (m, 2H); 4.22 (m, 1H): 4.42 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.39 (dd, 1H); 5.56 (dd, 1H); 6.01 (d, 1H) 6.39 (d, 1H)

Analogously, disilyl ether **122b** is converted into title compound **123b**.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.56 ppm (s, 3H); 0.79 (m, 2H); 0.85 (m, 2H); 0.94 (t, 3H); 1.02 (d, 3H); 3.78 (t, 1H); 3.93

(d, 1H); 4.13 (m, 2H); 4.22 (m, 1H); 4.42 (m, 1H); 5.00 (brs, 1H); 5.32 (brs, 1H); 5.45 (m, 2H); 6.01 (d, 1H); 6.39 (d, 1H)

20-Methyl-Series

Example 28

(5Z,7E,22E)-(1S,3R,24S)-20-Methyl-25-(4-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **126a** and (5Z,7E,22E)-(1S,3R,24R)-20-methyl-25-(4-methylthiazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol **126b**

640 mg of (5E,7E,22E)-(1S,3R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-20-methyl-9,10-secochola-5,7,10(19),22-tetraen-24-al **124** (WO 94/07853) is treated analogously to aldehyde **29**, and 620 mg of (5Z,7E,22E)-(1S,3R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-20-methyl-9,10-secochola-5,7,10(19),22-tetraen-24-al **125** is obtained as a colorless foam.
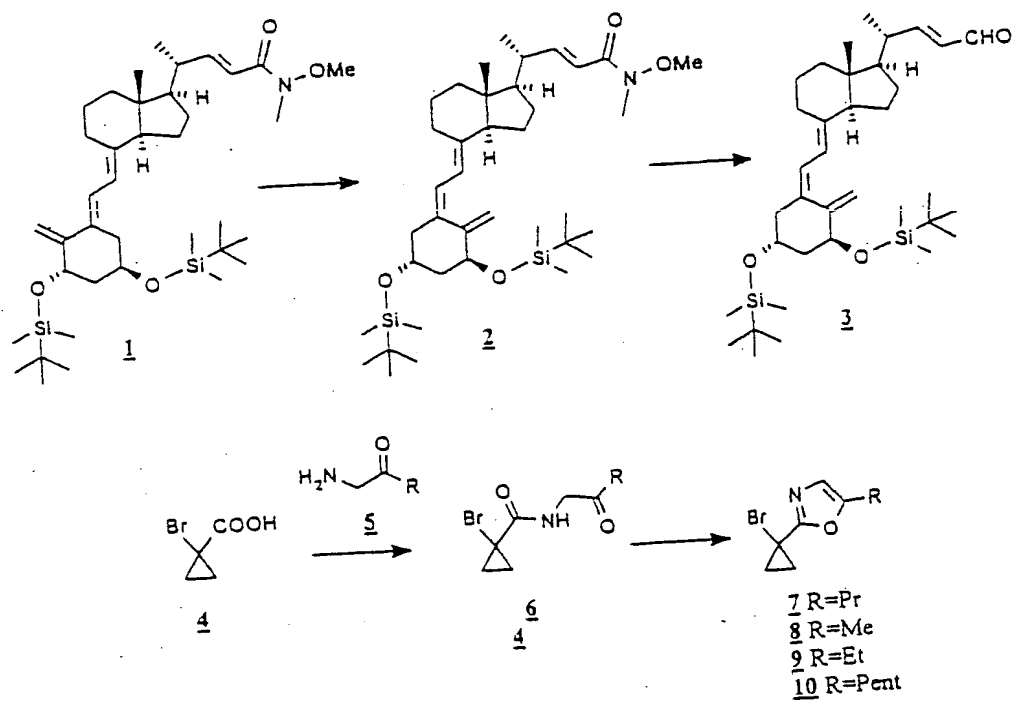
^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.05 ppm (s, 12H); 0.52 (s, 3H); 0.87 (s, 3H); 1.10 (s, 3H); 1.17 (s, 3H); 4.18 (m, 1H); 4.38 (m, 1H); 4.82 (brs, 1H); 5.18 (brs, 1H); 5.99 (d, 1H); 6.02 (dd, 1H); 6.20 (d, 1H); 7.00 (d, 1H); 9.52 (d, 1H)

Analogously to Example 5, aldehyde **125** is converted with 2-(1-bromocyclopropyl)-4-methylthiazole **18** into title compounds **126a** and **126b** which after chromatographic separation accumulate as colorless foams.

__126a:__ ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.50 ppm (s, 3H); 0.97 (s, 3H); 1.04 (s, 3H); 2.39 (s, 1H); 3.98 (d, 1H); 4.22 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.32 (dd, 1H); 5.33 (brs, 1H); 5.86 (d, 1H); 5.98 (d, 1H); 6.48 (d, 1H); 6.64 (s, 1H)
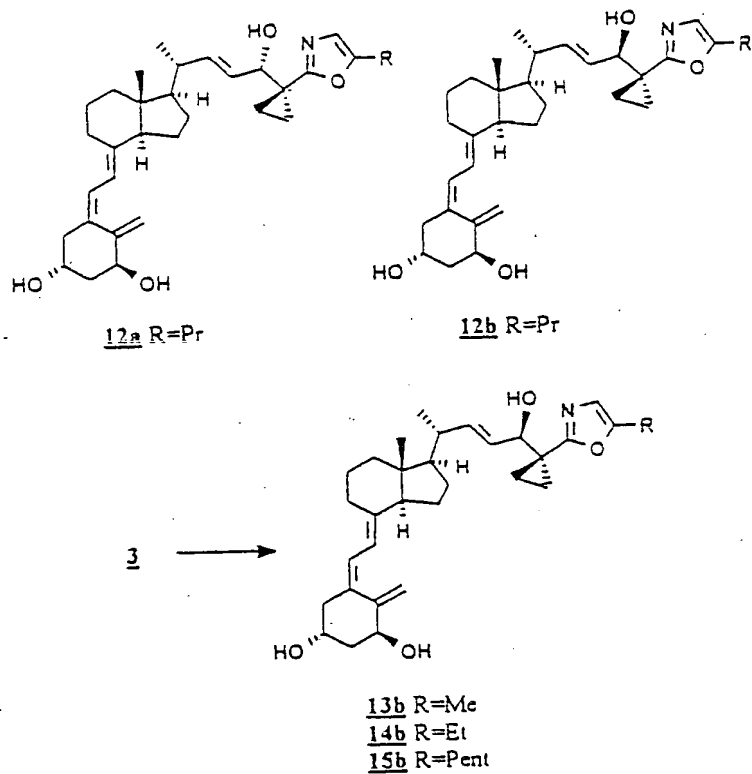
__126b:__ ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.49 ppm (s, 3H); 0.96 (s, 3H); 1.05 (s, 3H); 2.39 (s, 1H); 3.98 (d, 1H); 4.22 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.31 (dd, 1H); 5.33 (brs, 1H); 5.86 (d, 1H); 5.98 (d, 1H); 6.48 (d, 1H); 6.64 (s, 1H)

20-Epi Series

Example 29

(5Z,7E,22E)-(1S,3R,20S,24S)-25-(5-Butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol __131a__ and (5Z,7E,22E)-(1S,3R,20S,24R)-25-(5-butyloxazol-2-yl)-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-1,3,24-triol __131b__

2.1 g of (5E,7E)-(1S,3R,20R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-9,10-secopregna-5,7,10(19)-triene-20-carbaldehyde __127__ [M. J. Calverley, L. Binderup Bioorg. Med. Chem. Lett. __3,__ 1845 (1993)] is treated analogously to aldehyde __29,__ and 2.0 g of (5Z,7E)-(1S,3R,20R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-9,10-secopregna-5,7,10(19)-triene-20-carbaldehyde __128__ is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.05 ppm (s, 12H); 0.56 (s, 3H); 0.87 (s, 3H); 1.17 (d, 3H); 4.18 (m, 1H); 4.38 (m, 1H); 4.83 (brs, 1H); 5.18 (brs, 1H); 6.00 (d, 1H); 6.22 (d, 1H); 9.54 (d, 1H)

1.9 g of aldehyde **128** is introduced into 28 ml of toluene, 2.6 g of N-methoxy-N-methyl-2-(triphenylphosphoranylidene)-acetamide is added under nitrogen [D. A. Evans et al. **J. Am. Chem. Soc.** **112**, 7001 (1990)] and heated for 3 days to 80°C. After cooling, it is poured into water, extracted with ethyl acetate, dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 1.6 g of (5Z,7E,22E)-(1S,3R,20R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-N-methyl-N-methoxy-9,10-secochola-5,7,10(19),22-tetraen-24-amide **129** accumulates as a colorless foam.

1.4 g of amide **129** is dissolved in 25 ml of THF and cooled to -78°C under nitrogen. 10 ml of diisobutylaluminium solution (1 M in hexane) is added in drops, and it is stirred for 1 more hour. 0.8 ml of methanol is now added in drops, and the mixture is allowed to reach room temperature. The reaction mixture is now poured into potassium-sodium tartrate solution, extracted with ethyl acetate, and the organic phase is dried on sodium sulfate and concentrated by evaporation. The residue is chromatographed on silica gel with ethyl acetate/hexane, whereby 1.1 g of (5Z,7E,22E)-(1S,3R,20R)-1,3-bis[[dimethyl(1,1-dimethylethyl)silyl]oxy]-9,10-secochola-5,7,10(19),22-tetraen-24-al **130** is obtained as a colorless foam.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.05 ppm (s, 12H); 0.53 (s, 3H); 0.87 (s, 3H); 1.10 (d, 3H); 4.20 (m, 1H); 4.39 (m, 1H); 4.85 (brs, 1H); 5.20 (brs, 1H); 6.00 (d, 1H); 6.10 (dd, 1H); 6.22 (d, 1H); 6.79 (dd, 1H); 9.53 (d, 1H)

Analogously to Example 16, aldehyde **130** is converted with 2-(1-bromocyclopropyl)-5-butyloxazole **87** into title compounds **131a** and **131b** which after chromatographic separation accumulate as colorless foams.

131a: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.56 ppm (s, 3H); 0.90 (t, 3H); 0.96 (m, 2H); 1.11 (d, 3H); 1.15 (m, 2H); 2.57 (s, 3H); 4.10 (d, 1H); 4.22 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.33 (brs, 1H); 5.41 (dd, 1H); 5.58 (dd, 1H); 6.00 (d, 1H); 6.37 (d, 1H); 6.57 (s, 1H)

131a: ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 0.57 ppm (s, 3H); 0.90 (t, 3H); 0.97 (m, 2H); 1.10 (d, 3H); 1.15 (m, 2H); 2.58 (s, 3H); 4.10 (d, 1H); 4.22 (m, 1H); 4.43 (m, 1H); 5.00 (brs, 1H); 5.33 (brs, 1H); 5.42 (dd, 1H); 5.53 (dd, 1H); 6.00 (d, 1H); 6.38 (d, 1H); 6.58 (s, 1H)

Starting Materials in the 5-Alkyloxazole Series

5-Alkyloxazole Derivatives

12a R=Pr

12b R=Pr

3 →

13b R=Me
14b R=Et
15b R=Pent

Starting Materials in the 4-Alkylthiazole Series

4

16

4

17 R=Et
18 R=Me
19 R=Pr
20 R=Bu

4-Alkylthiazole Derivatives

21a R=Et

21b R=Et

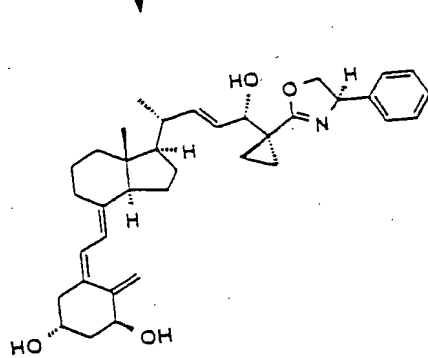**22a** R=Et

22b R=Et

23b R=Me
24b R=Pr
25b R=Bu

Starting Materials in the Phenyl Series

26   27   28

Phenyl Derivatives

29   30   + 28   31

32   33

34a

34b

35a

35b

Starting Materials in the 4-Alkylphenyl Series

36

37

38

39

40

41

42

43

44

45

46

47

4-Alkylphenyl Derivatives
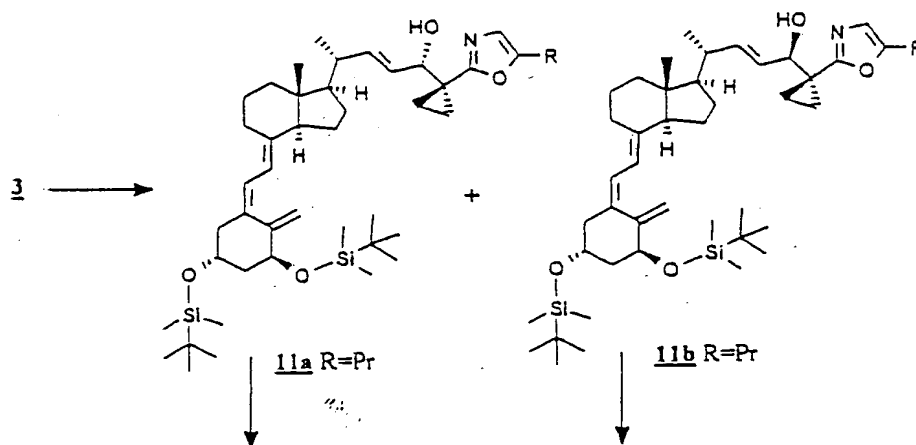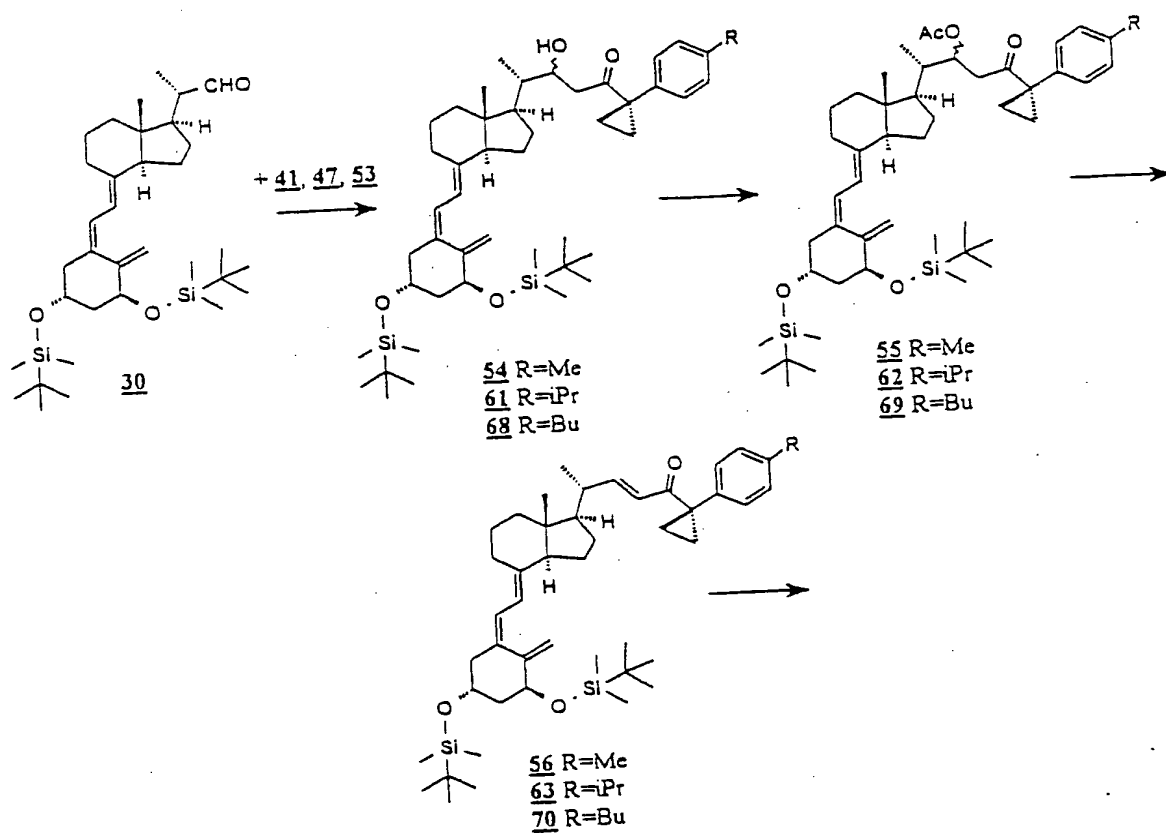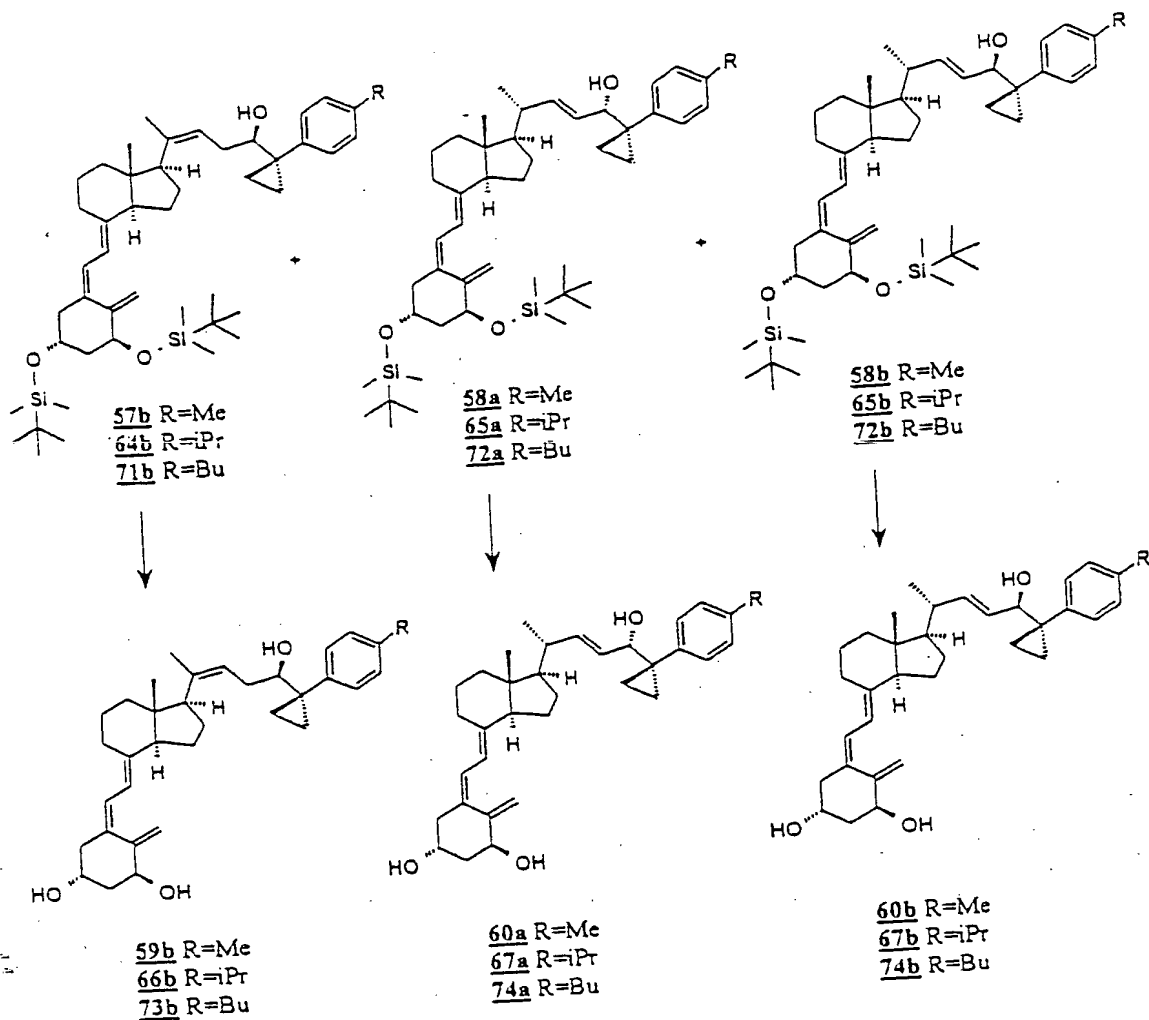
Starting Materials in the 4-Alkyloxazole Series

4-Alkyloxazole Series

82a R=Me

82b R=Me

83a R=Me
84a R=Et
85a R=Pr

83b R=Me
84b R=Et
85b R=Pr
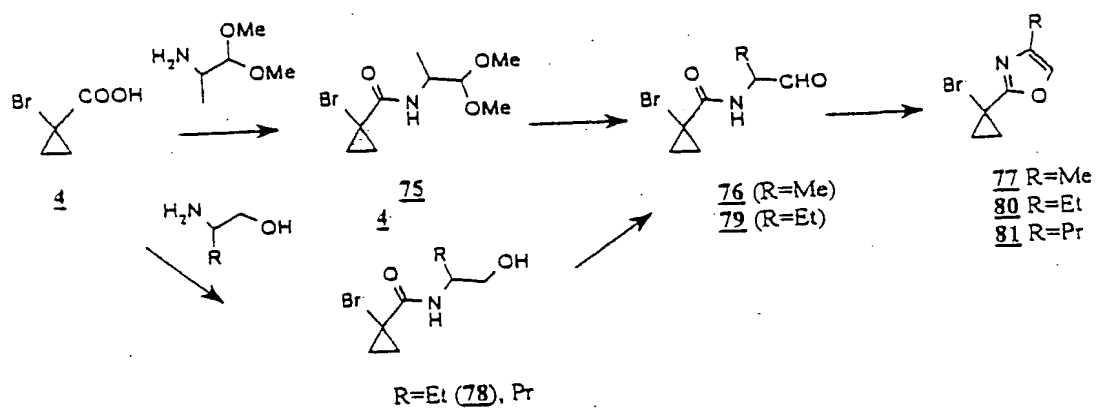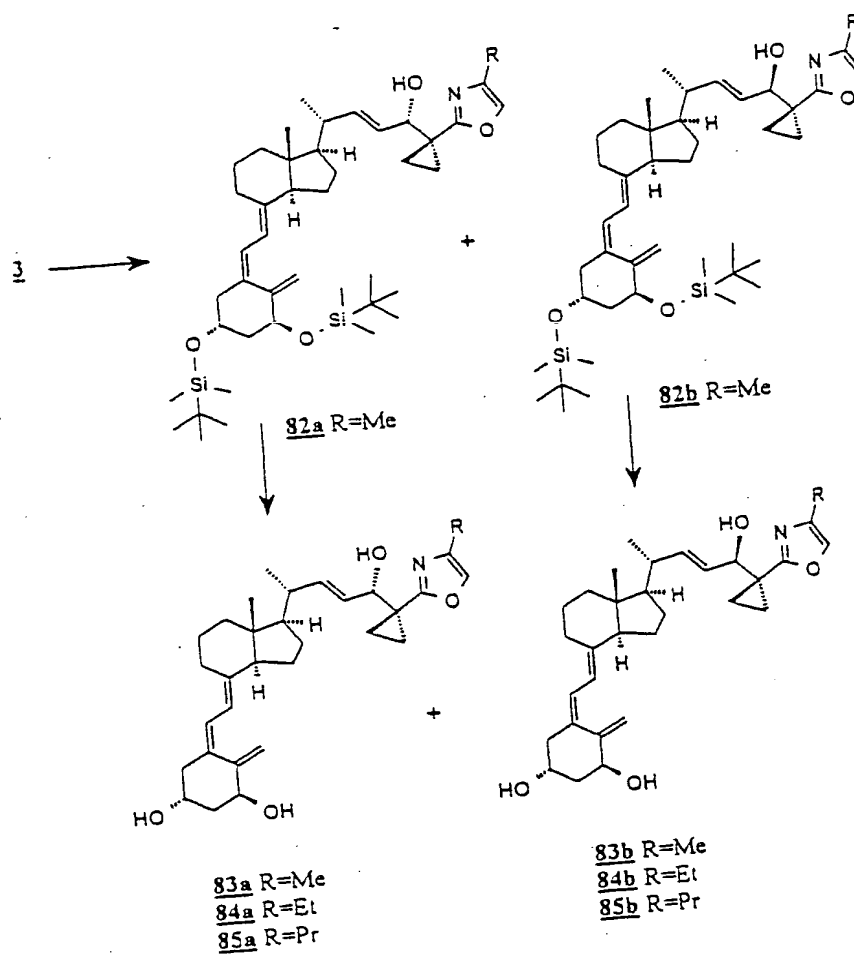
5-Butyloxazole Derivative

4

86 R=Bu
4

87

88b
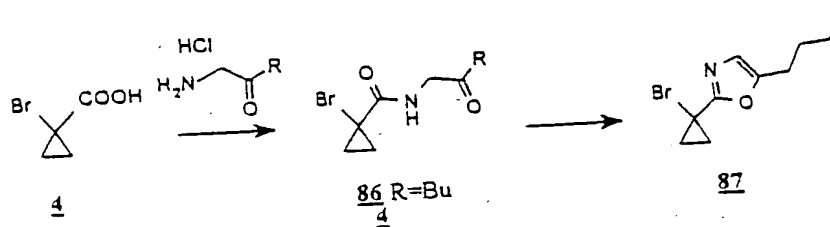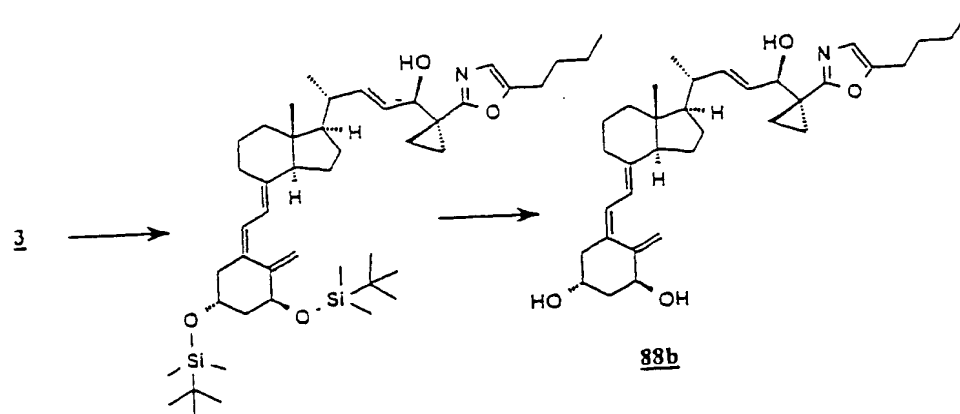
Starting Materials for the 5-Alkylthiazole Series
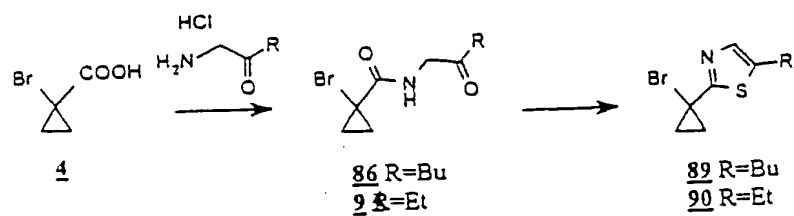
4

86 R=Bu
9ᵃ R=Et

89 R=Bu
90 R=Et

5-Alkylthiazole Series

3 →

91a R=Bu

+

91b R=Bu

92a R=Bu
93a R=Et

92b R=Bu
93b R=Et

1,2,4-Oxadiazole Series

94a

95a R=Bu

94b

95b R=Bu
96b R=Et
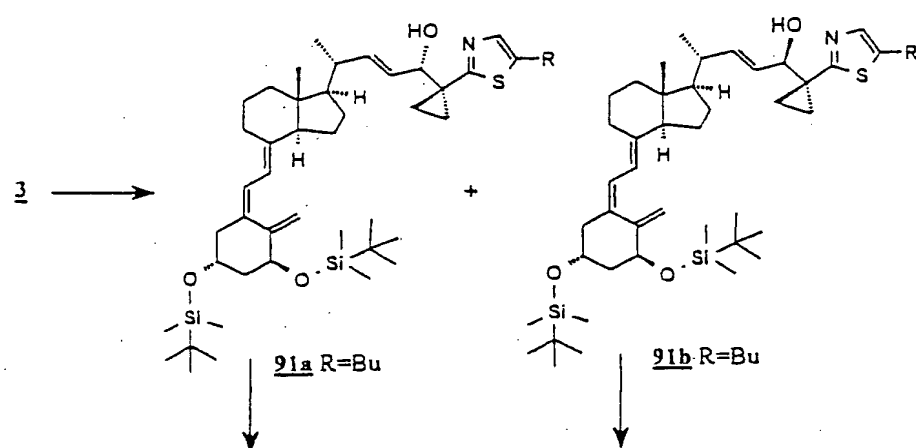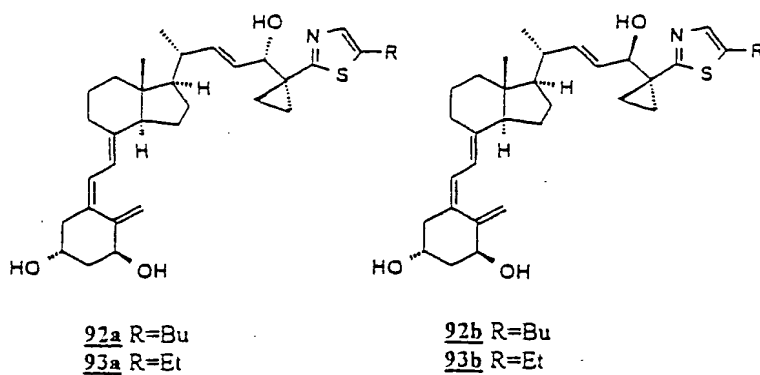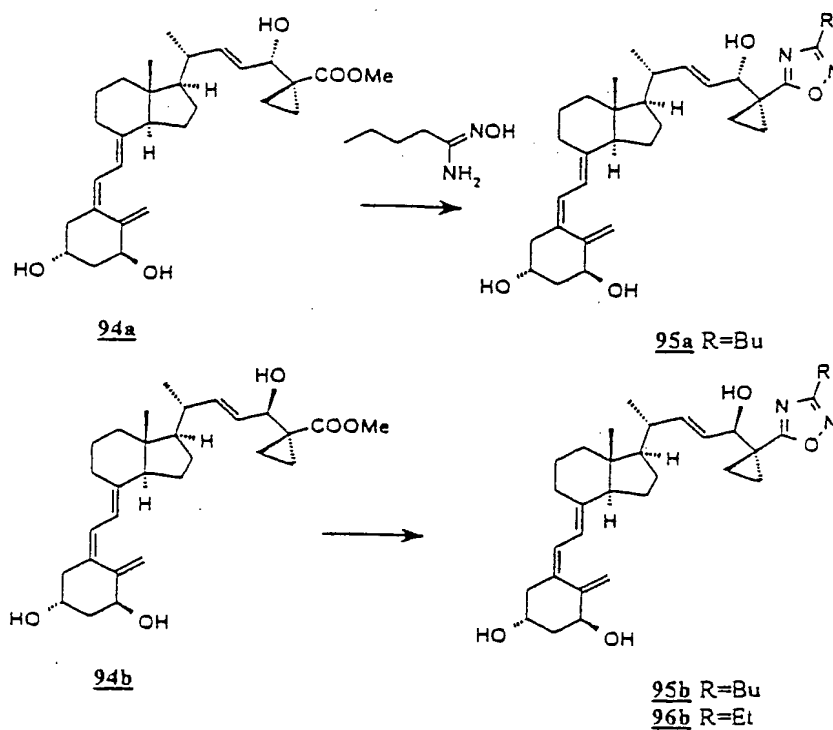
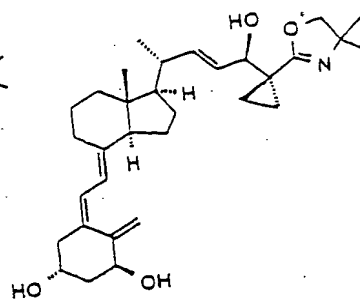## Starting Materials for the 25-Pyridyl Series

25-Pyridyl Series
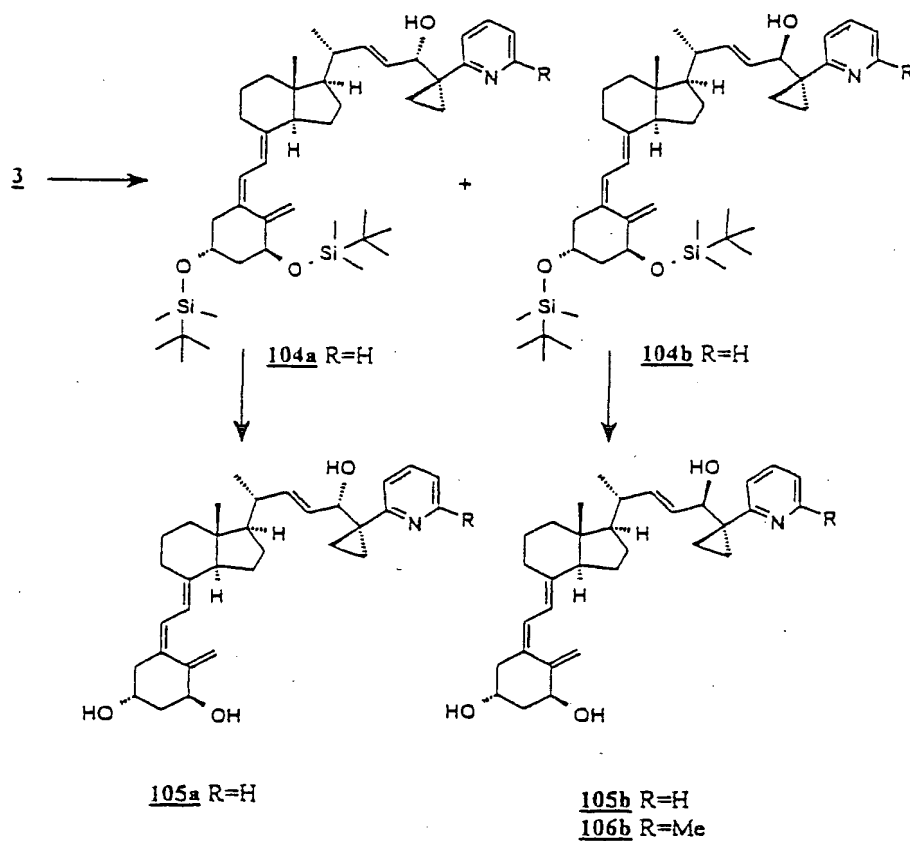
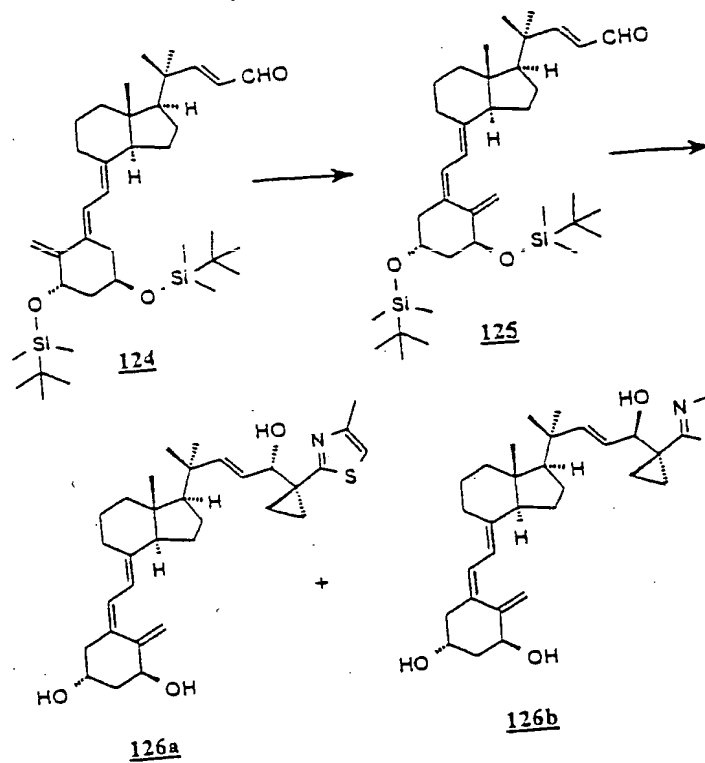## Starting Materials in the 25-Oxazoline Series

25-Oxazoline Series

117a

117b

3 →

118a

+

118b

119a

119b

20-Methyl Series

124

125

126a

+

126b

20-Epi Series

127

128

129

130

131a

131b